VOLUME 8 NUMBER 3

ARCHIVES OF PATHOLOGY

SEPTEMBER, 1929

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, Jan. 25, [illegible] the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for [illegible] at special rate of postage provided for in the Act of Feb. [illegible], authorized Jan. 25, 1926.

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AUGUST, 1929.

ARCHIVES OF PATHOLOGY

VOLUME 8 SEPTEMBER, 1929 NUMBER 3

THE SO-CALLED SMALL ROUND CELL INFILTRATIONS

II. SYPHILIS OF THE CENTRAL NERVOUS SYSTEM *

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In a previous contribution on the subject of round cell infiltrations in polioencephalitis and acute epidemic encephalitis,[1] we were able to demonstrate that the vast majority of the infiltrating elements in the adventitial spaces, as well as those encountered in the extravascular territory, are constituted of emigrated lymphocytes, large mononuclears (monocytes) and homoplastic derivatives of the emigrated cells. It was pointed out that in none of the cases investigated was there any evidence of a cytogenic activity on the part of the fixed adventitial connective tissue or of vascular endothelium sharing in the production of the perivascular infiltrations. It was also shown that the emigrated lymphoid cells, after extravasation, varied in their behavior. Some of them remained unchanged as lymphocytes and large mononuclears; others differentiated into either polyblasts, macrophages or compound granular cells, and occasionally into plasma cells, the polyblasts being the prevailing cell type into which they were transformed.

REVIEW OF LITERATURE

DERIVATION OF INFLAMMATORY MONONUCLEAR CELLS

Since the writing of our last paper, several interesting contributions have been made on the specificity and the alleged cytopoietic activity of

* Submitted for publication, May 3, 1929.

* Read before the Forty-Fifth Session of the American Association of Anatomists, Rochester, N. Y., March 27, 1929.

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* This work was aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Michels, N. A., and Globus, J. H.: So-Called Small Round Cell Infiltrations; Polio-Encephalitis and Acute Epidemic Encephalitis, Arch. Path. **4**:692 (Nov.) 1927.

the vascular endothelium. Thus, the contention of Foot and Herzog, that carbon laden endothelial cells may desquamate from the lining of small blood vessels and capillary tubes and become free ameboid cells, has been proved to be unwarranted by Lang [2] and by Stilwell.[3] The latter, repeating Herzog's experiment on the living frog, noted that the carbon particles passing through the fixed endothelium were taken up by adjoining mononuclear cells, which thereupon differentiated into free ameboid polyblasts. Lang [4] came to a similar conclusion in his studies on the inflammatory reactions of the connective tissue and the omentum in rabbits that had received intravenous injections of india ink. Earlier, in explants of lung inoculated with tubercle bacilli, Lang [5] observed that the dust cells, i. e., macrophages or epithelioid cells, took their origin not from the capillary endothelium but from small interlobar septal histiocytes.

Recently, Foot [6] retracted his views on the endotheliogenous derivation of large mononuclears. Lewis,[7] on using a supravital staining technic in the study of sterile inflammations of the deep fascia of the rat, found no evidence that mononuclears and macrophages are derived either from endothelium or connective tissue.

Clarke and Clarke,[8] studying the living cells and tissues in the transparent tail fin of amphibian larvae, stated that a desquamation of lymphatic endothelium occasionally took place, but that the process was "in no sense a proliferation of endothelium to form free leukocytes and wandering cells." They concluded, "In none of our observations on the normal growth of lymphatic and blood capillaries and on their behaviour under experimental conditions, such as inflammation, did we see the slightest evidences for the formation of 'endothelial leucocytes.'"

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2. Lang, F.: Rôle of Endothelium in the Production of Polyblasts (Mononuclear Wandering Cells) in Inflammation, Arch. Path. **1**:41 (Jan.) 1926.

3. Stilwell, F.: On the Phagocytic Capacity of the Blood Vessel Endothelium of the Frog's Tongue and Its Presumed Transformation Into Wandering Cells, Folia haemat. **33**:81, 1926.

4. Lang, F.: Ueber Gewebskulturen der Lunge, Arch. f. exper. Zellforsch. **2**:93, 1926.

5. Lang, F.: The Reaction of Lung Tissue to Tuberculous Infection in Vitro, J. Infect. Dis. **37**:430, 1925.

6. Foot, N. C.: Studies on Endothelial Reactions, etc., Am. J. Path. **3**:413, 1927.

7. Lewis, W. H.: Macrophages of the Deep Fascia of the Thigh of the Rat in Spreads Supravitally Stained with Neutral Red and with Janus Green, Tr. Am. A. Anatomists, 42nd session, New Haven Anat. Rec. **32**:215, 1926; Macrophages in Sterile Inflammation of Deep Fascia of the Rat, ibid. **32**:215, 1926.

8. Clarke, E. R., and Clarke, E. L.: On the Failure of Endothelial Cells, Even After Desquamation, to be Transformed into Wandering Cells, with Observations on the Nature of Endothelium, Anat. Rec. **36**:357, 1927.

Recently, Bloom,[9] a former assistant of Maximow, in an extensive treatise on the monocyte, categorically denied a histiocytic, especially a reticulo-endothelial, origin of the monocyte. His work was based on the monocytosis experimentally produced in rabbits by infection with *Bacillus monocytogenes* and by injections of india ink, lithium carmine and saccharated iron oxide. In his investigations, he used supravitally stained smears of blood and of various organs, wet fixed smears of blood and of organs and sectioned material. He admitted a transformation of fixed embryonic reticulum cells into free macrophages, but insisted that these were not identical with monocytes. Differentiation of the latter proceeded from lymphocytes within the blood vessels, especially those of the spleen and the liver. The monoblast, as a specific stem cell (Ferrata, Sabin, Witts and Webb), does not exist. In his own words, "I have never observed any evidence of the direct transformation of any fixed cells, be they fibroblast or reticulum or endothelial cells of embryonic or mature nature into monocytes."

On the other hand, there is a notable array of recent investigations that reaffirm the endothelial activity. Thus, according to Oeller and Töppich, vascular endothelium is activated cytogenetically after anaphylactic shock. Oeller [10] maintained that in guinea-pigs rendered allergic through the injection of chicken erythrocytes, subsequent intravenous injections of antigen produced an intense and almost immediate (in from fifteen to thirty minutes), largely amitotic proliferation of the vascular endothelium in the lungs and other organs, the products being free ameboid cells, of which many differentiated into granulocytes.

A similar behavior of the vascular endothelium in guinea-pigs after intratracheal and intravenous injections of tubercle bacilli was described by Töppich.[11] Recently, Sabin, Doan and Cunningham,[12] by using the supravital technic on films of living cells, which were obtained by punctures of the spleen and the peritoneum of the living rabbit, and on spreads from the omentum and subcutaneous tissue, were able to detect

9. Bloom, W.: The Origin and Nature of the Monocyte, Folia haemat. **37**:1, 1928; The Relationships Between Lymphocytes, Monocytes and Plasma Cells, Folia haemat. **37**:63, 1928.

10. Oeller, H.: Die funktionelle Bedeutung der Gefässwandzellen bei akuten Infektionen, Med. Klin. **19**:97, 1923; Experimentelle Studien zur pathologischen Physiologie des Mesenchyme und seiner Stoffwechselleistungen bei Infektionen, Krankheitsforschung **1**:28, 1925.

11. Töppich, G.: Die zellulären Abwehrvorgänge in der Lunge bei Erst und Wiederinfektion mit Tuberkelbazillen, Krankheitsforschung **2**:15, 1925; Die örtliche Zellbindung in Gefässwänden und im Bindegewebe, München. med. Wchnschr. **74**:135, 1927.

12. Sabin, F.; Doan, C., and Cunningham, R.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, Contrib. Embryol., 82, Carnegie Inst., Washington **16**:125, 1925.

two distinct types of phagocytic cells, viz., clasmatocytes and monocytes. The former, they contended, were derived from the endothelium, mainly that of the spleen. They added, however, that "whether there is a widespread origin of clasmatocytes from the endothelium of the peripheral capillaries is not yet certain."

McJunkin,[13] on the basis of phagocytosis of india ink in vitro, peroxidase staining of smears and sections with benzidine, supravital staining with neutral red and injections of india ink, distinguished three types of phagocytes: (1) monocytes or benzidine-positive mononuclears, which are present in the blood, the bone-marrow and the spleen only; (2) lympho-endotheliocytes, benzidine-negative, which arise from the lymphatic reticulo-endothelium and are normally present in the blood stream; (3) hemendotheliocytes, benzidine-negative, which are normally absent in the circulation, but which appear under pathologic conditions, and which arise from the endothelium of capillary blood vessels.

Di Guglielmo [14] noted in the peripheral blood of patients with acute erythremia and streptococcemia large numbers of "endothelial phagocytes." These cells were distinct from monocytes and hemohistiocytes. They phagocytosed bacteria and showed mitotic proliferation. In his opinion, the vascular endothelium was responsible for their genesis and because of this he regarded their presence in large numbers in the circulating blood as warranting the term "endotheliosis." Di Guglielmo, describing the histologic changes observed in smears and sections of bone-marrow, spleen and liver in cases of erythremia and septicemia, maintained that in both conditions there was prevalent a generalized hypertrophy and hyperplasia of the reticulo-endothelial system, and that vessels of the lungs and kidneys exhibited hypertrophy and detachment of vascular endothelial cells, which, when free in the lumen of the vessels, acquired a phagocytic function. The author contended that since they were morphologically identical with those observed in the peripheral blood, the cytopoietic and functional activity of the vascular endothelium is general and hence it should be regarded as part of the reticulo-endothelial system.

Fontana,[15] in his extensive monograph on endocarditis lenta, maintained that in 39 per cent of the cases investigated by him the first drop of peripheral blood obtained soon after rubbing an area punctured

13. McJunkin, F. A.: Identification of Three Types of Mononuclear Phagocytes in the Peripheral Blood, Arch. Int. Med. **36**:799 (Dec.) 1925.

14. Di Guglielmo, G.: La patologia e la clinica del sistema reticolo-endoteliale, Haematologica **7**:481, 1926.

15. Fontana, F.: Ricerche su di uno speciale reperto ematologico nella endocardite lenta e su reperti affini in varie altre condizioni, Haematologica **7**:271, 1926.

(notably in the ear region) showed the presence of endothelial and lymphocytoid cells, which frequently showed phagocytic properties. Successive drops contained fewer of these structures and when no rubbing preceded the procuring of blood, they were sparse or entirely lacking. They commonly occurred in ratios varying from 0.5 per cent to 18.2 per cent, but sometimes attained a ratio of 34.3 per cent. In similar preparations of blood from twelve normal persons and from ninety-eight patients with diseases other than endocarditis lenta, the endothelial elements were extremely sparse and more often lacking entirely. Their presence in a relatively high ratio in endocarditis lenta was believed to be pathognomonic of this disease. The proliferation and desquamation of the peripheral capillary and precapillary endothelium was thought to be their source of origin.

Schilling,[16] on the basis of transitional stages between histiocytes and monocytes in the blood in cases of endocarditis lenta and monocytic leukemia and on that of identical negative oxydase reactions and phagocytosis in the two cells, derived the monocytes from the stellate Kupffer cells of the liver.

Esposito,[17] studying twenty cases of typhoid fever, encountered a limited number (from one to three, or 0.5 per cent) of circulating "reticulo-endothelial" elements. Previous rubbing of the area from which the blood was taken (ear), however, did not increase their ratio (Fontana) and hence he concluded that a local origin of the structures from vascular endothelium is highly improbable.

Capocaccia,[18] with repeated massive injections of trypan blue and oxy-saccharate of iron oxide into rabbits and guinea-pigs, obtained a monocytosis, the endothelial forms of which he assumed to be products of vascular endothelium.

According to Masugi,[19] a pupil of Aschoff, an initial storing of colloidal substance causes a proliferation of the reticulo-endothelial system, but later when the entire system is actively storing, leading to a "blockade," desquamation with formation of monocytes takes place. Mature, dye-storing histiocytes, however, never participate in the production of monocytes.

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16. Schilling, V.: Der Monocyte in trialistischer Auffassung und seine Bedeutung im Krankheitsbilde, Med. Klin. **22**:563, 1926.

17. Esposito, A.: Sulle cellule reticolo-endoteliali nei sangue circolante dei tifosi, Haematologica **9**:157, 1928.

18. Capocaccia, M.: L'apparato reticolo endoteliale; le modificazioni del quadro ematologico negli animali trattati con injezioni di trypanblau e di saccarato ossido di ferro, Haematologica **8**:321, 1927.

19. Masugi, M.: Ueber die Beziehungen zwischen Monozyten und Histiocyten, Beitr. z. path. Anat. u. z. allg. Path. **76**:396, 1927.

Claussen,[20] studying miliary tuberculosis of the kidneys in cows and pigs, found that the endothelial cells of the interlobular capillaries were (in addition to the histiocytes) participating in the formation of the epithelioid cells characteristic of the tubercles.

The subject of so-called endotheliocytopoiesis became recently somewhat more clouded by the amazing contentions of von Möllendorff,[21] and his students Koll [22] and Knake,[23] who asserted that fixed fibroblasts are mainly responsible for the genesis of the various types of the free cells found in inflammatory conditions.

Von Möllendorff's opinion is based on the observations made on the inflammatory reaction of loose connective tissue in mice and rabbits following subcutaneous injections of trypan blue. The loose connective tissue, in his opinion, consists of an abundantly meshed fibrocyte network containing numerous resting wandering cells. The latter are attached to the net by fine strands which, in inflammatory conditions may break and so release the cells, which transform themselves into macrophages. Tissue leukocytes, also, he said, are similarly generated from the net through vacuolization in the nuclei of fibroblasts and differentiation of cytoplasmic granules. In acute inflammations, a widespread breaking up of the net takes place with the resulting formation of many round cells (polyblasts). These in a large measure differentiate into polymorphonuclears which soon undergo degeneration. A number of surviving large cell types (histiocytes) regenerate the syncytium by spreading out and by amitotic proliferation. The adventitial cells are not parent cells in the sense of Marchand, but represent simply a more or less torn portion of the fibrocytic net. Thus, von Möllendorff would consider the connective tissue as morphologically and biologically identical with that of the reticulo-endothelial system.

Koll, using subcutaneous injections of Patentblau, noted that in mice the "inflammatory centers" showed an immediate degeneration of the original leukocytes, which was followed by a decided heteroplastic regeneration of the leukocytes from fibroblasts by a rounding up of histiocytes. Two days later, changes in the newly formed leukocytes gave rise to

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20. Claussen: Untersuchungen über die Histogenese des Nierentuberkels, Virchows Arch. f. path. Anat. **266**:456, 1927.

21. Von Möllendorff, W. and M.: Das Fibrozyten-Netz im lockeren Bindegewebe seine Wandlungsfähigkeit und Anteilnehme am Stoffwechsel, Ztschr. f. Zellforsch. u mikr. Anat. **3**:503, 1926; Die ortliche Zellbildung in Gefässwänden und im Bindegewebe, München. med. Wchnschr. **74**:135, 1927.

22. Koll, W.: Bindegewebsstudien: II. Die Wirkung von Patentblau auf das Unterhautbindegewebe der Maus, Ztschr. f. Zellforsch. u. mikr. Anat. **4**:702, 1927.

23. Knake, C.: Bindegewebsstudien; die Histio- und Leukozytenentstehung bei Tuschewirkung auf das lockere Bindegewebe des Kaninchens, Ztschr. f. Zellforsch. u. mikr. Anat. **5**:208, 1927.

macrophages. But, in his conclusions, he said that "the rôle played by emigration in the increase of leukocytes was not investigated."

Knake maintained that in rabbits, after subcutaneous injections of india ink, dye-laden fibroblasts rounded themselves up and differentiated into histiocytes and round cells, both of which might develop into polymorphonuclear leukocytes through a differentiation of eosinophil granules and a gradual liberation of carbon particles. At the beginning of the inflammatory process, the walls of the small veins showed a marked "transformation" into round cells; in addition to the "completer" leukocytes, numerous intergrades were present. While he did not exclude the possibility of an emigration of leukocytes (which he regarded as still an open question), he favored a local origin of the inflammatory cells through differentiation and amitotic proliferation of fibroblasts. In respect to emigration, Knake stated, "Wie gross demnach wirklich die Anzahl der 'emigrierten' Leukocyten ist, lässt sich vorerst nicht abschätzen." (It cannot yet be estimated how large the number of emigrated leukocytes really is.)

This view of von Möllendorff and his students as to the polyvalent hemohistiopoietic potencies of the fibroblasts has since received a decided and well merited check. Using von Möllendorff's own technic, Maximow [24] conducted control experiments, compared his results with von Möllendorff's original slides and concluded that "new facts were not discovered." Subcutaneous injections of trypan blue or india ink revealed the familiar pictures of an inflammatory reaction to a soluble or a particulate foreign substance. Nothing was observed that could suggest the possibility of the origin of leukocytes from fibroblasts.

More recently von Möllendorff, to substantiate his claim, conducted a series of experiments. In collaboration with Burger,[25] he separated the jugular vein from surrounding tissue, ligated it and then introduced various irritating substances. Sections of this vein were then explanted. Within an hour there resulted a strong leukocytosis in the wall and in perivascular spaces with a transformation of endothelium and vascular connective tissue elements into leukocytes. No difference was observable between cultured and noncultured sections.

Gerlach and Jores,[26] repeating von Möllendorff's experiments, emphatically denied the latter's contention. Irritants, such as lamb serum, turpentine or jequiritol III, were introduced into the jugular vein

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24. Maximow, A.: Morphology of the Mesenchymal Reactions, Arch. Path. **4**:567 (Oct.) 1927.

25. Von Möllendorff, W.: Die örtliche Zellbildung in Gefässwänden und im Bindegewebe, München. med. Wchnschr. **74**:135, 1927.

26. Gerlach, W., and Jores, A.: Die Herkunft der Exudatleukocyten bei der akuten Entzündung, Virchows Arch. f. path. Anat. **267**:551, 1928.

in guinea-pigs. After a double ligation, portions of the vein were investigated at various intervals of from one to ten and three-quarter minutes; others were explanted. In both, the sequence of events was as follows: aggregation of blood cells, stagnation, marginal attachment of leukocytes to endothelium and subsequent emigration of these out into the tissue. Neither the vascular endothelium nor the constituents of the vessel wall gave rise to an exudate of leukocytes. Similar results were obtained in sensitized rabbits rendered aleukocytic through repeated subcutaneous injections of benzol-olive oil and in untreated rabbits rendered poor in leukocytes through subcutaneous injections of staphylococci, jequiritol I and turpentine. The excised tissues showed no evidence of a local origin of the leukocytic exudate. Their presence about the vessels and in the surrounding tissues (at times, marked) must be traced to hemic elements that reached the site of inflammation by diapedesis.

Thus, the discussion as to the derivation of the inflammatory mononuclear cells has, for the present, shifted from the endothelium to the fibroblasts, von Möllendorff, attempting, as Maximow put it, "to revolutionize completely the dominant ideas on the morphology of local defense reaction."

HISTOLOGIC CHANGES IN SYPHILITIC DISEASES OF THE CENTRAL NERVOUS SYSTEM

As material for our second paper on the small round cell infiltration, we have selected various types of syphilitic diseases of the central nervous system.

Difficult and markedly polemic have been the steps leading to the present knowledge of the histologic changes in these diseases. Syphilis, in particular, came in for considerable discussion, because cases were frequently reported in which the important evidence of a preexisting primary lesion was either entirely lacking or not sufficiently substantiated. On the other hand, instances of known nonsyphilitic origin in which the clinical pictures simulated those of paresis were frequently mistaken for syphilis. Finally, the possibility of a co-existing nonsyphilitic form of encephalitis in cases of known or doubtful syphilis was not sufficiently taken note of.

Alzheimer's Views Concerning Paresis.—The pioneer and still dominant work in the establishment of the histologic features of paresis and of meningovascular syphilis is the monograph of Alzheimer.[27] It is based on a study of 320 cases of various brain disturbances, 70 of which were diagnosed clinically as paresis. Since this work is not

27. Alzheimer, A.: Histologische Studien zur Differenzialdiagnose der progressiven Paralyse, in Histologische und Histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1904, vol. 1, pp. 18-314.

generally known to the general pathologist or anatomist, a résumé of Alzheimer's views is hereby given as an introduction to our own observations.

Alzheimer emphasized the fact that syphilis cerebri presents no uniform histologic picture, while the anatomic alterations in paresis are so characteristic that even in the absence of a clinical diagnosis one can readily identify this disease. The latter is a chronic inflammatory process, and exhibits in all instances a widely distributed, fairly uniform adventitial infiltration with plasma cells and lymphocytes throughout the cerebral cortex. It is also characterized by changes in the vessels, hypertrophy of the intima, formation of endothelial sprouts, glial hypertrophy, degeneration of nerve fibers and fiber tracts and formation of rod cells. These changes may occur also in the brain stem, including the basal ganglions, thalamus, midbrain, pons and medulla oblongata; but, in these areas, their origin is not fully established.

The essential process of paresis, as understood by Alzheimer, is a degeneration of the parenchyma of the central nervous system, associated with progressive and regressive changes in the blood vessels. It is typified by the following alterations:

1. Hypertrophy of the endothelium with a marked tendency to the formation of new vessels through budding of the hypertrophied intima. As a result there is a marked increase of the number of blood vessels, more pronounced in some cases than in others. It is never lacking, save in the acute stages of the disease.

2. An increase of the elastic tissue with a formation of new meshes around the swollen endothelium, resulting in the formation of stronger walls.

3. Hypertrophy of the adventitia. This is always present, and is sometimes pronounced.

4. Widening and infiltration of the adventitial spaces. Most abundant among the infiltrating elements are the plasma cells; they are never lacking, not even in the acute type of the disease. Next in frequency are the lymphocytes, with mast cells occurring as isolated units.

5. Regularly a regressive change is noted in many of the vessels, especially those in marginal zones of the cortex. It may lead to a complete obliteration of the vessel and a hyalinization of its walls. If the latter occurs it is a secondary phenomenon.

6. Rod cells are constant in the cortex and their presence is pathognomonic of the disease. (Alzheimer's view that they originate from the vessels has since been definitely abandoned, their microglial derivation having been established.)

Most pronounced among the changes in the ectodermal structures is the marked hyperplasia and hypertrophy of the glia cells. These, in turn, give rise to an increase of glia fibers. The newly formed glia strengthens the walls of the blood vessels and gives rise to a thicker covering over the surface of the cortex. In advanced cases, the glia hems in the already heavily infiltrated vessels. Regressive changes occur also in the glia cells, which undergo sclerosis, pigmentation and

vacuolization. Necrobiosis of nerve cells, according to Alzheimer, leads to a gradual disappearance of the cortical fiber tracts. This is so characteristic that it may be regarded as specific for paresis. Topographically, the disease progresses along nerve tracts, resulting frequently in degeneration of definite fiber tracts in the cisternal area. Rapid disintegration of nerve cells and early replacement with massive glia hypertrophy is characteristic of paresis.

Meningeal changes are a constant phenomenon. No case of paresis is entirely free of them, though in the earlier stages of the disease pial thickening and infiltration need not necessarily be marked. The pial changes consist of hypertrophy of the endothelium, partial regressive changes in vessels and isolated new formation of capillaries. There is a massive increase of collagenous fibers, and hypertrophy of fibroblasts, some of which show regressive changes. In the arachnoid meshes and about the pial blood vessels there are infiltrating elements, most predominant among which are the plasma cells; some of these show signs of metamorphosis and vacuolization of their cytoplasm, simulating gitter cells. Mixed with the plasma cells are lymphocytes, mast cells and occasional well formed gitter cells. Polymorphonuclears are few or lacking.

These histologic changes were strikingly stereotyped in 170 cases clinically diagnosed as paresis. For syphilis cerebri, the situation is entirely different; here no uniform picture is found. This, as explained by Alzheimer, is due to the fact that in this disease the lesions in the cerebral cortex are not essentially primary as in paresis, but secondary. They appear to be subsequent to a previous pial disturbance. It is for this reason that in syphilitic meningitis the cortical layer next to the pia is most affected and the lesions gradually become less and less frequent as they recede from the periphery. Once brain tissue is involved, however, the lymphocytic infiltration advances rapidly and may quantitatively surpass that of paresis. Thus in meningovascular syphilis the degree of infiltration is much greater than in the severest form of paresis. The infiltration may be so marked as to obliterate all boundaries between the pia and the cortex, a condition best explained by the fact that the exudative cells do not, as in paresis, retain a perivascular habit, but filter out into neighboring tissue. If, however, the meningeal alterations remain restricted, changes in the cortex are correspondingly limited.

In syphilis cerebri there are also a new formation of vessels, a swelling of the intima, an increase of adventitial cells, a hyperplasia and hypertrophy of glia cells and a degeneration of ectodermal components. The typical plasma cells, according to Alzheimer, are decidedly less frequent in this disease than in paresis, their place being taken by a cell type intermediate between the lymphocyte and the plasma cell.

Appended to Alzheimer's work is the equally important contribution by Nissl,[28] in which he presented views substantially in agreement with those of Alzheimer. Nissl took up the problem of the origin of the infiltrating cells and evaluating the then prevalent theories as to their histogenous or hematogenous origin, he said that since a transformation of hypertrophied vascular connective tissue cells (endothelium, adventitial cells) into lymphocytes or plasma cells was never encountered in the extensive material investigated by him, the exudate cells must be regarded as hemic in origin; i.e., they represent emigrated lymphocytes, the plasma cells being special differentiation products of the latter.

As against Havet's [29] contemporary contribution that plasma cell infiltrations may be encountered in disturbances of the brain other than paresis, Nissl maintained that in his study of over 200 such cases he was unable to find a single instance presenting a typical infiltration with plasma cells. Conceding the point that the occurrence of the latter of itself is not necessarily pathognomic of paresis, the absence of plasma cells, in his opinion, certainly rules out paresis.

The Plasma Cell.—Since the plasma cell holds an important place among the infiltrating elements in the cases to be described, a short review of the literature on this type of cell is hereby given.

The morphology, genetic relationship and pathologic significance of the plasma cell have been the objects of considerable investigation and discussion. The extensive literature is highly controversial, as readily may be seen from the comprehensive review of this subject by Downey.[30] In summarizing the data, it may be noted that the term plasma cell was first used by Waldeyer in 1875 to describe certain types of connective tissue cells that gave a deep staining reaction with the then newly discovered basic aniline dyes of Ehrlich. The term, as now applied, was first used by Unna [31] in his description of cell elements encountered in lupus of the skin, though one year previously Ramon y Cajal [32] had independently called attention to the cell type, the representatives of which he then termed the chromatophil or cyanophil elements.

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28. Nissl, F.: Zur Histopathologie der paralytischen Rindererkrankung, in Alzheimer: Histologische und Histopathologische Arbeite über die Grosshirnrinde, Jena, Gustav Fischer, 1904, vol. 1, pp. 315-494.

29. Havet, T.: Des lésions vasculaires du cerveau dans la paralysie générale, Bull. Acad. roy. de méd. de Belgique (4 série) **16**:503, 1902.

30. Downey, H.: The Origin and Structure of the Plasma Cell of Normal Vertebrates, Especially of the Cold Blood Vertebrates, and the Eosinophils of the Lung of Amblystoma, Folia haemat. **11**:275, 1911.

31. Unna, P.: Ueber Plasmazellen, insbesondere beim Lupus, Monatsch. f. prakt. Dermat. **19**:465, 1891.

32. Ramon y Cajal, cited from Ferrata: Le Emopatie, Milano, Societa Editrice Libraria, 1918.

Unna originally defined the plasma cell as an extremely large structure having a deeply basophil protoplasm with a typical, fine, nonmetachromatic granulation (granuloplasm). He regarded it as a hypertrophied connective tissue cell found only under pathologic conditions, mainly in chronic inflammatory reactions.

Marschalko,[33] making his observations on normal, pathologic and experimental material, further delimited the term. He characterized the cell as containing (1) a nonhomogenous basic protoplasm with frequent paranuclear semilunar lighter staining areas, and (2) an eccentric position of the nucleus, which encloses angular blocks of chromatin (from 5 to 8), arranged in a circle about the nuclear membrane. Since these patterns of the chromatin were similar to that of the spokes of a wheel, Pappenheim advocated the term "Radkern." Though upholding Unna's specificity of the plasma cell, Marschalko differed with him in regard to its origin. In the opinion of Marschalko, plasma cells represented transformed emigrated lymphocytes; and their formation was not necessarily pathologic. In his opinion, they represented normal constituents of the connective tissue and the blood-forming organs. Jolly (1900) was among the first to confirm this view in his assertion that the cells could easily be demonstrated in peritoneal membranes.

The opposing views of Unna and Marschalko led subsequent investigators to take the following positions regarding the origin of the plasma cell: 1. A histogenous origin from connective tissue cells (Unna, 1891-1907; Ramon y Cajal, 1906; Veratti, 1905; Marchand, 1901; Dominici; Foa, 1902; Greggio; Ferrata, 1918; Joannovice, 1889 [only partly]). 2. A hematogenous origin from emigrated lymphocytes (Baumgarten, 1890; Helly; Krompecher, 1898; Marschalko, 1895; Nissl, 1904; Jolly, 1923, and Naegeli, 1919). 3. Mixed origin from emigrated lymphocytes or pre-existent tissue lymphocytes (Ribbert, 1897; Joannovice, 1899; Pappenheim, 1901; Maximow, 1902; Schridde, 1905; Weidenreich, 1911; Downey, 1911; Dubreuil and Favre, 1920; Bloom, 1928).[34]

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33. Marschalko, T.: Ueber die sogenannten Plasmazellen, ein Beitrag zur Kenntnis der Herkunft der entzündlichen Infiltrationszellen, Arch. f. Dermat. u. Syph. **30**:241, 1895.

34. A more complete review of the literature will be found in the paper by Downey (footnote 30) and in the following: Weidenreich, F.: Die Leukocyten und verwandte Zellformen, Wiesbaden, J. F. Bergmann, 1911; Ztschr. f. d. ges. Anat., p. 3; Ergebn. d. Anat. u. Entwcklngsgesch. **19**:527, 1911. Ferrata, A.: Le Emopatie, Milano, Societa Editrice Libraria, 1918, vol. 1, and 1923, vol. 2, (parte speciale). Jolly, J.: Traite technique d'hématologie, Paris, A. Maloine et fils, 1923. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923. Maximow, A.: Bindegewebe und blutbildende Gewebe, Handbuch der Mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 2, Die Gewebe, pt. 1.

The fibroblastic origin of the plasma cells as suggested by Unna and Cajal has never been fully established. The question of their origin from clasmatocytes, resting wandering cells, adventitial cells or hemohistioblasts is one intimately associated with the problem of the tissue lymphocytes. But since, as Maximow in his recent work conclusively showed, the modern hematologists need no longer distinguish between histogenous and hematogenous lymphocytes, the origin of the plasma cell may definitely be traced to the differentiating small and medium-sized lymphocytes, monocytes and polyblasts, which acquire a deep basophilia, especially in the peripheral zone of the cytoplasm, and develop a lighter staining paranuclear area. The latter, according to Maximow (1902), Weidenreich, Wallgren and Jolly, constitutes a sphere of attraction for the cell's centrosome group as demonstrated by iron-hematoxylin staining.

The "Radkern" pattern of the nucleus (Marschalko) and the eccentric position of the nucleus were soon discarded as essential features. While the plasma cells are particularly numerous under pathologic conditions, the observations of Jolly, Maximow, Weidenreich, Downey, Ferrata and others have shown that they are a normal component of the general connective tissue particularly that of the omentum and of the blood-forming organs. They are frequently found in the mucosa of the digestive tract, as well as in the interstitial tissue of various glands and organs (mammary, submaxillary, tonsils, liver, kidney). In respect to the origin of the massive aggregates of plasma cells in chronic inflammatory conditions, Jolly (1923) held that "it must be admitted that the lymphocytes from which they are formed have come from the blood by diapedesis." An identical position was held by Maximow (1927) in the statement that in the foci of small cell infiltrations in chronic inflammations there are lymphocytes with transitional forms in the process of plasma cell formation.

It may be added that Weidenreich and Downey believed that the plasma cells are but temporal functional stages of the lymphocytes, while Jolly, Maximow and others contended that the cells are transient structures in the sense that they are brought into existence only to undergo degeneration, often resulting in the production of acidophilic bodies, commonly known as Russell bodies.

OBSERVATIONS

MATERIALS AND METHODS

The material for the present studies consisted of a group of seven cases, three of which were clinically diagnosed as chronic parenchymatous syphilitic encephalitis (paresis), three as meningovascular syphilis and one as vascular syphilis cerebri.

Numerous blocks of tissue were taken from various parts of the brain and spinal cord, including the cerebrum, midbrain, cerebellum, pons, medulla and, in some instances, the hypophysis, semilunar ganglion and dura mater.

Most of the material was fixed in formaldehyde. In one case, Zenker's fluid was used. The paraffin embedded blocks were sectioned at an average thickness of 5 microns. Delafield's hematoxylin followed by the azure-eosin combination as employed by Maximow was the staining method. Sections were placed in a

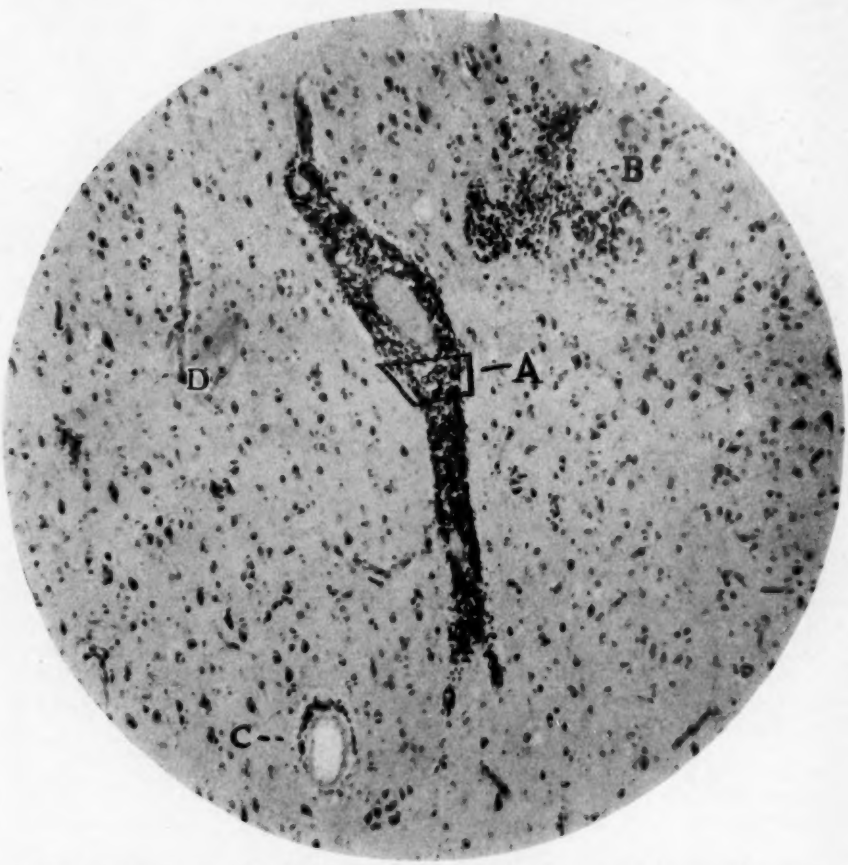

Fig. 1 (case 1).—Typical maximal infiltration in chronic parenchymatous syphilitic encephalitis. The region designated *a* appears again in figure 2; *b* indicates a new formation of capillaries with an infiltration of ameboid lymphocytes, polyblasts and plasma cells; *c* indicates an infiltration from two to three cell rows in depth; *d* indicates a new-formed capillary; × 100.

diluted solution of hematoxylin (wine color) over night, washed the following day (for from eight to ten hours) in distilled water and transferred over night into the following stain: azure II in 1:1,000 solution, 9 cc.; eosin W. G. (Grübler) in 1:1,000 solution, 17 cc.; distilled water, 100 cc. Sections were differentiated in 95 per cent alcohol, dehydrated in two changes of absolute alcohol cleared in two changes of xylene and mounted in dammar.

CASE 1. CHRONIC PARENCHYMATOUS SYPHILITIC ENCEPHALITIS (PARESIS)

The perivascular infiltrations here frequently attain the intensity encountered in poliencephalitis and acute epidemic encephalitis (figs. 1 and 2). Striking features, however, are the nonlymphoid aspect of the general parenchyma, the absence of the streamlike orientation of migrated lymphoid cells away from the vessels and the decided alteration in the architectural organization of the cortical layers caused by a widespread new formation of capillary tubes.

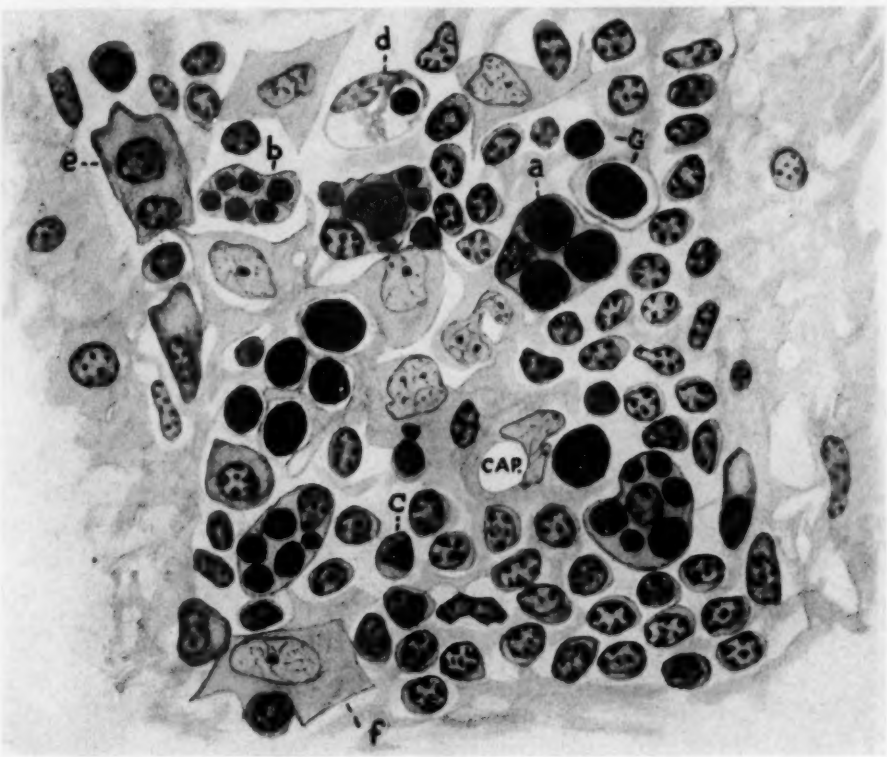

Fig. 2.—The area marked *a* in figure 1. The letters *a*, *b*, and *d* designate Russell bodies enclosed in degenerating plasma cells; *c* a dividing plasma cell; *f* a detached endothelial cell assuming the fibroblast form, and *g* free Russell bodies.

The maximal infiltrations reach a depth of from eight to ten rows, somewhat less therefore than that seen in poliencephalitis, in which as many as fifteen rows are often encountered. While the precapillary venules average from two to four rows, the capillaries show more often the single row of infiltration. Such single rows are for the most part intermittently interrupted (figs. 3, 4 and 5). Not infrequently, therefore, stretches of capillary tubes may be seen in which infiltrating elements are extremely sparse or lacking. This is particularly true of the recently formed capillaries (figs. 5 and 6).

Initial infiltrations are best observed in the capillary regions (fig. 3). In poliencephalitis, the single row infiltrations consist predominantly of small lymphocytes and present a uniform marginal radial seriation, but here they contain nearly exclusively plasma cells, two or three of which are, as a rule, disposed about cross sections of capillaries in a semicircular fashion (fig. 25 *A*). In longitudinal view, their habitat frequently appears as in figure 5, where the cell (*a*) either completely overlaps the capillary wall or (*b*) covers the vessel only partially. This seems to

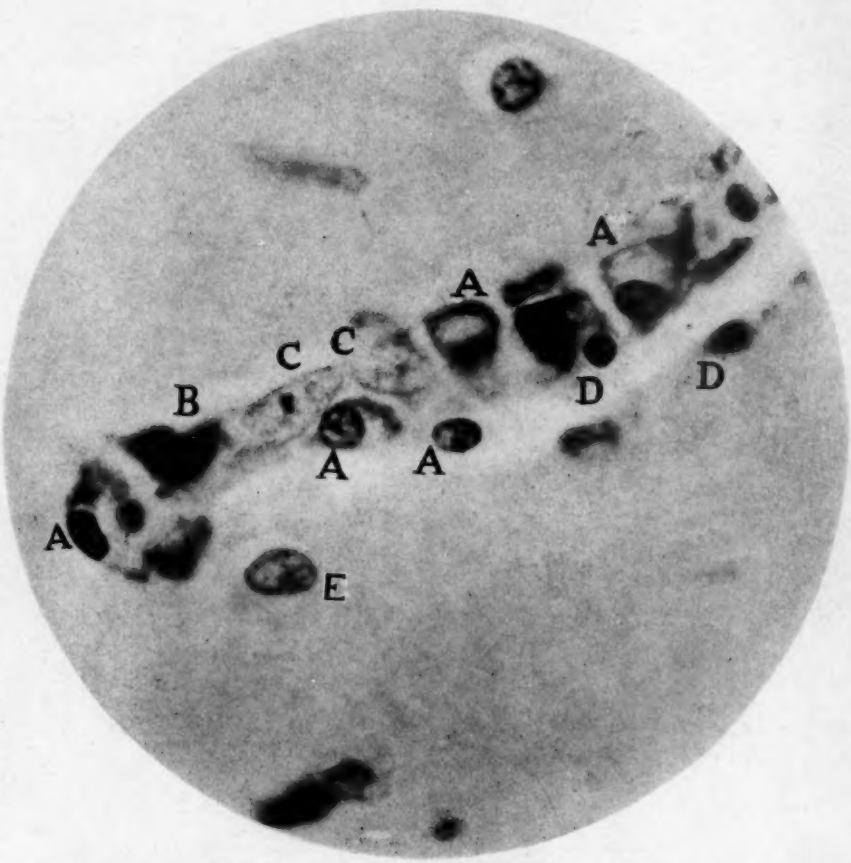

Fig. 3.—A capillary showing an initial infiltration mainly with plasma cells. The letter *a* indicates a plasma cell, *b* a detached endothelial cell, *c* a hypertrophied endothelial cell, *d* a small lymphocyte and *e* a glia cell; × 1,200.

indicate that in initial infiltrations the plasma cells tend to remain in close proximity to the endothelial wall (fig. 3).

The plasma cells are extremely polymorphous. Their nuclei are usually round, often oval; most frequently they are eccentric in position. The cell bodies are frequently oblong in outline, often simulating the so-called adventitial cells of Marchand. They also assume spindle, box and triangular shapes. When closely packed, they are usually polygonal, but when separated, they show the spherical form.

Isolated mast cells are frequently founud in initial infiltrations (fig. 25 *A*). In the absence of mesodermal elements, other than the endothelial cells, which do not form mast cells, they are in all probability hemic in origin and represent a differentiation product of the plasma cells. They are the so-called plasmamast cell of Krompecher,[35] which was also described by Marschalko, Pappenheim, Weidenreich, Downey and recently by Dubreuil and Favre[36] (1921). While in some instances mast cells are situated close to the endothelium and simulate the fixed histogenous form of mast cell (fig. 5) they, nevertheless, in the majority of cases, retain some features of their previous plasma cell morphology; the polygonal contour of the cytoplasm, the lighter, usually nongranular perinuclear area and the characteristic eccentric position of the nucleus (fig. 25 *B*). Similar structures are also observed in the larger infiltrations.

The sparsity of lymphocytes in the initial infiltrations may be explained by the probability that immediately after diapedesis the lymphocytes change into plasma

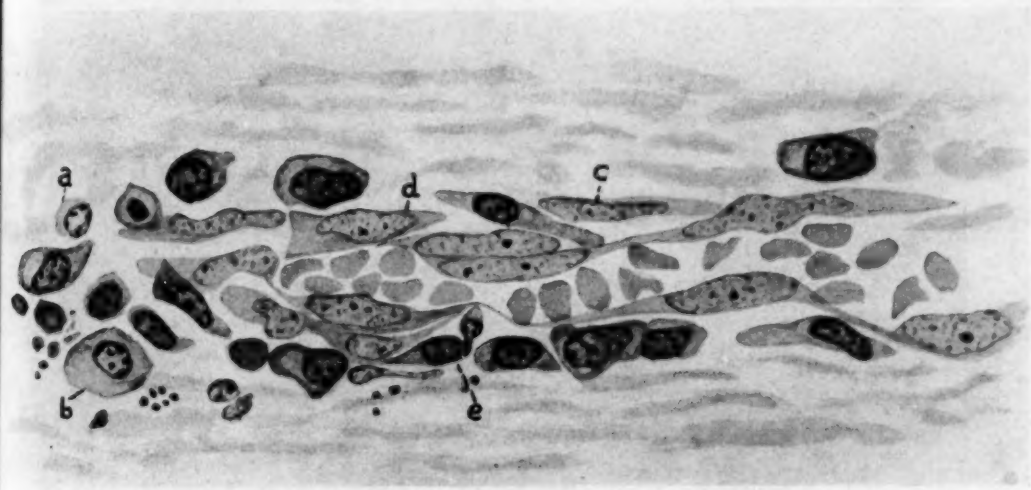

Fig. 4.—Initial infiltration; *a* indicates a degenerating small lymphocyte or plasma cell, *b* a degenerating plasma cell, *c* a detached endothelial cell retaining its normal form, *d* a detached endothelial cell undergoing change into a fibroblast-like structure, and *e* a recently emigrated large mononuclear changing into a plasma cell.

cells. This is supported by the observation that the protoplasm of the lymphocytes, while in transit through the capillary wall or immediately thereafter, often assumes a deeper basophilia (fig. 5 *d*).

Lymphocytes are more numerous in the more intensive infiltrations (fig. 7). When the latter attain the proportion of from four to six rows, lymphocytes constitute approximately half of the infiltrating elements. In the maximal infiltrations (ten or more rows), lymphocytes abound and frequently exceed the number of plasma cells (fig. 2). These small and medium sized lymphocytes predominate

35. Krompecher, E.: Beiträge zur Lehere von den Plasmazellen, Beitr. z. path. Anat. u. z. allg. Path. **24**:163, 1894.

36. Dubreuil, G., and Favre, M.: Cellules plasmatique, plasma granulations spécifiques, cellules a corps de Russell, Arch. d'anat. micr. **17**:302, 1920-1921.

(figs. 2 and 7) and there are but few large lymphocytes or large mononuclears, a decided departure from what is observed in poliencephalitis and acute epidemic encephalitis. In paresis, the larger types of cells are mainly plasma cells, suggesting the probability that the extravasated lymphocytes undergo rapid differentiation into plasma cells. This explains the presence of many small and medium-sized lymphocytes in which the deeply basophilic protoplasm, the perinuclear portion of which is varyingly lighter in staining reaction, seems to indicate transitional stages between lymphocytes and plasm cells (fig. 7). In this process of transformation, the nucleus is commonly displaced from its central position, its chromatin is broken up into triangular masses, which are radially disposed and lodged against the nuclear membrane, thus presenting the typical nuclear pattern of Marschalko. However, it may retain its original contour. Since there are lymphocytes that acquire the typical nuclear form of Marschalko but retain the

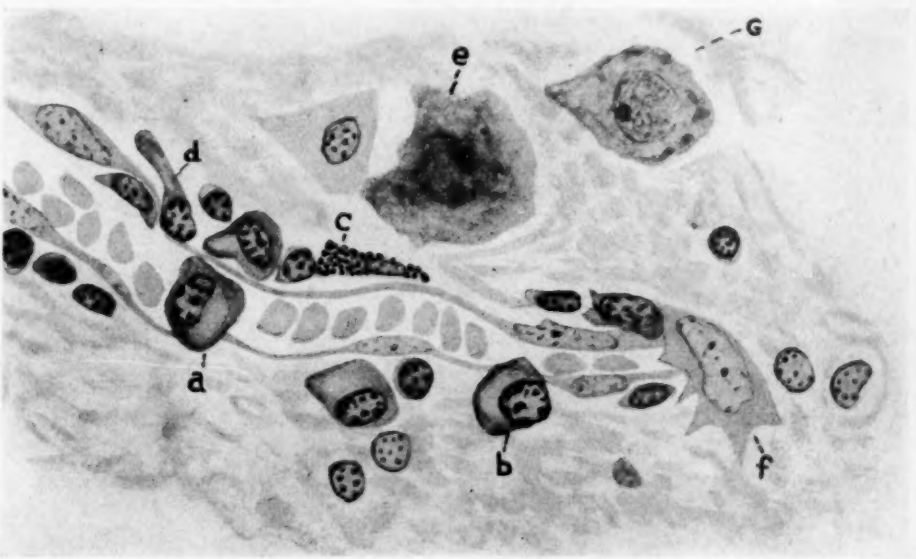

Fig. 5.—A newly formed capillary in chronic parenchymatous syphilitic encephalitis. The letter *a* indicates a plasma cell completely overlapping the capillary wall, *b* a plasma cell partly overlapping the capillary wall, *c* a plasma-mast cell, *d* a recently emigrated lymphocyte acquiring the plasma cell basophilia, *e* a degenerating glia cell, *f* a detached endothelial cell assuming the fibroblast-like structure and *g* a degenerating nerve cell.

cytoplasmic basophilia (the type lymphocyte of Marschalko), it appears that the essential changes in the differentiation of lymphocytes into plasma cells are not to be sought in an alteration of nuclear architecture alone, but also in the development of a deeper basophilia on the part of the cytoplasm. Associated with the latter is another fairly constant alteration—the formation of one or more lighter cytoplasmic areas (fig. 7) which often fuse into a continuous paranuclear zone.

The change in the basophilia of the protoplasm in small lymphocytes may be sudden (fig. 7 *a*) or gradual and synchronous with a progressive increase of cell body (fig. 7 *c*). The fully differentiated plasma cell usually has a peripheral rim

of protoplasm that stains deeper than the rest of the body cytoplasm (fig. 7 *d*). Such rims are encountered even in the smaller type of lymphocytes undergoing differentiation into plasma cells.

The large lymphocytes and large mononuclears, aside from those forming plasma cells, often change into polyblast-like structures (fig. 7 *c*) and macrophages (fig. 25 *C*). The latter contain phagocytosed pigment matter. Such macrophages are occasionally the predominant cell type of the infiltrates about small veins where they reach a depth of from one to three rows. Fully differentiated plasma cells not infrequently change into plasmamast cells, but are rarely seen to take on the character of macrophages.

It would seem that the plasma cell is a final differentiation product and not a temporary functional condition of the lymphocyte as claimed by Weidenreich and Downey, for many plasma cells are found in a process of degeneration, shown by the reduced staining affinities of the nucleus and the cytoplasm, the rarefication

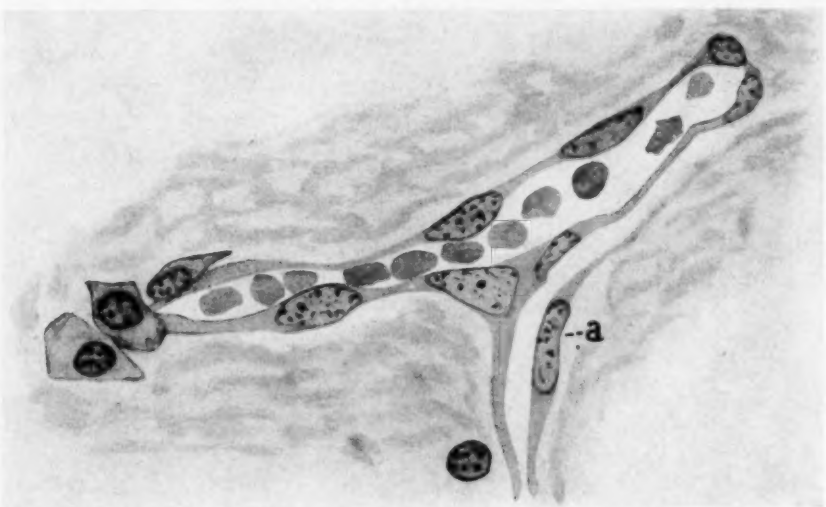

Fig. 6.—A budding newly formed blood vessel; *a* indicates free endothelial cell from an aborted capillary side sprout.

of the chromatin network and the distortion and marked vacuolization of the cytoplasm (fig. 4).

With progressive degeneration, the basophilia of the protoplasm becomes less and less pronounced, and the nuclei become pyknotic. During the degeneration of the plasma cell there frequently occurs a formation of acidophilic bodies, variously known as Russell bodies, "fuchsinophil bodies" or "hyaline bodies." They are usually of the size of an erythrocyte, but often attain giant proportions (fig. 2), most probably as the result of fusion of the smaller bodies. Thin protoplasmic strands may completely encircle the body or loop it in a horseshoe fashion. At necrobiosis, the bodies are set free in the tissue (fig. 2).

In their earlier stages, Russell bodies are represented by cytoplasmic enclosures of coarse eosinophilic granules simulating to a large extent an eosinophil type of granulation (fig. 25 *E*). They are not tissue eosinophils, for their protoplasm is deeply basophilic, while that of the eosinophils is distinctly oxyphilic. The cells

may, however, erroneously be mistaken for ripening plasmamast cells. But since the staining reaction of the Russell granules is never metachromatically basophilic but always decidedly acidophilic, we have means at hand for discrimination between the two types. The cause of the formation of Russell bodies is not known, though their frequent occurrence in various chronic inflammatory processes in which plasma cells predominate opens the way for speculation.

The massive degeneration is not limited to plasma cells, for the entire infiltrating group, including lymphocytes, large mononuclears and plasmamast cells, often undergoes cellular alterations with the formation of pigmented cells having

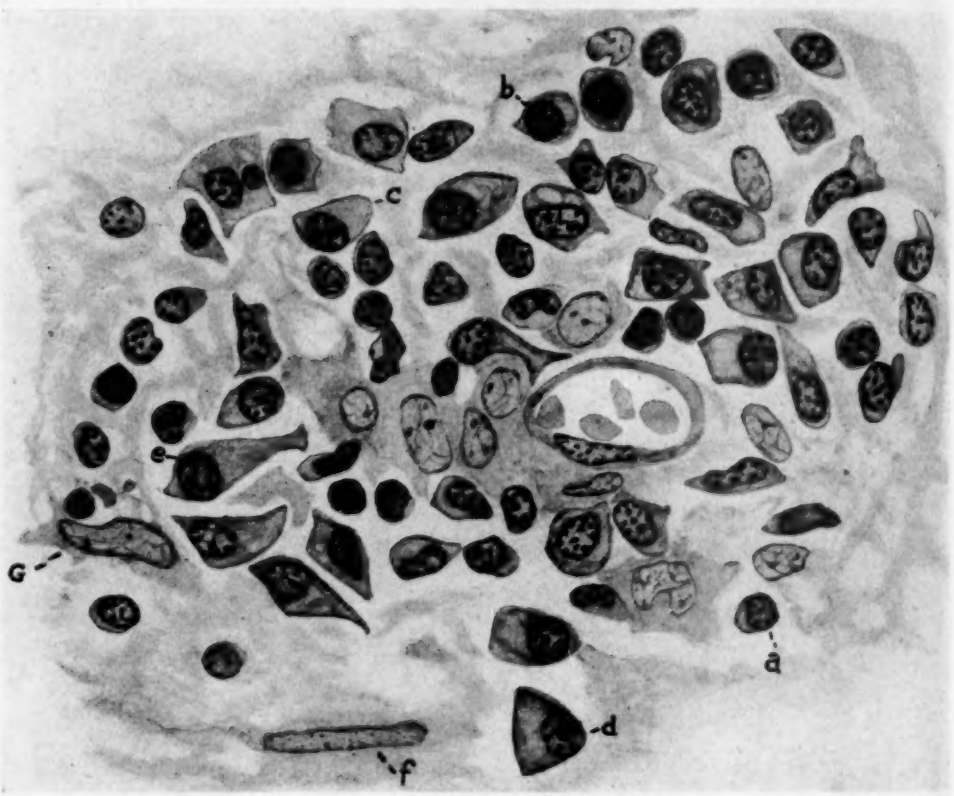

Fig. 7.—An area of intensive infiltration in chronic parenchymatous syphilitic encephalitis; *a, b, c* and *d* are lymphocytes undergoing differentiation into plasma cells; *e* is a polyblast, *f* a rod cell and *g* a detached endothelial cell.

pyknotic nuclei. The blood vessels, too, occasionally show similar regressive changes in all of their cellular components, viz., muscles, connective tissue and endothelium, with the result that the lumen of the vessels involved may become occluded with the cellular débris.

Cells in Emigration.—Active emigration of the infiltrating cells is frequently observed, so that it may be concluded that the vast majority of the infiltrating cells have a hemic origin. The cells in transit through the capillary wall are predominantly lymphocytes (small, medium, large) (fig. 25 *C* and fig. 8). The

emigrating large mononuclears, so frequently seen in poliencephalitis, are decidedly less numerous here as an emigrating cell (fig. 25 *D*).

The changes in the outlines of both the nucleus and the cytoplasm while the cells are forcing their way through the endothelium to an extravascular habitat are extremely varied and striking. The process frequently leads to distortion of the nuclear material into deeply staining dumb-bell shape structures, or in many instances into long flagellum-like protrusions, the proximal end of which is still in the lumen, and finally may effect a more or less prolonged imprisonment of both nucleus and cytoplasm in the endothelial cell through which the emigrating cell is attempting to pass (fig. 9 *a*).

After emigration, the behavior of the lymphoid cell varies. If it is a small lymphocyte, it may immediately hypertrophy and differentiate into a plasma cell. This is most commonly the case in capillary regions, in which small lymphocytes

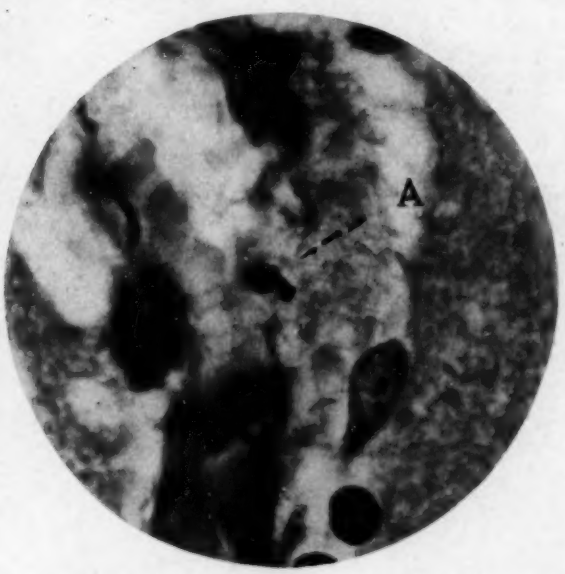

Fig. 8.—An emigrating small lymphocyte is shown at *a*; × 1,500.

are relatively rare. In the larger infiltrations of six or more rows (figs. 2 and 7) small lymphocytes may retain their original intravascular morphology, or may hypertrophy and differentiate into plasma cells, polyblasts and even macrophages. Emigrating large mononuclears, for the most part, seemingly differentiate immediately into plasma cells or macrophages, for rarely do the infiltrations show unmodified hemic large mononuclears (monocytes). Mitosis is a frequent occurrence both in medium-sized lymphocytes and in large mononuclears.

Mitotic division in the larger plasma cells is rare. When encountered, it is nearly exclusively in the small and medium-sized lymphocytes (fig. 2 *c*). The conclusion seems warranted that mitosis ceases when differentiation into plasma cells is completed. Plasma cells are frequently binucleate (fig. 2 *e*), occasionally trinucleate and multinucleate, a condition most probably associated with the aged or functional condition (amebism) of the cell rather than indicative of amitosis, as currently claimed by von Möllendorff for the fibroblast.

Cells in Extravascular Territory.—The alterations in the parenchyma in extravascular territory are totally different from those observed in either poliencephalitis or acute epidemic encephalitis. The focal infiltrations so characteristic of the last two conditions are almost entirely lacking. The nearest approximation to it are areas showing a meshlike neoformation of capillaries, in the midst of which one may find aggregations of hemic elements (lymphocytes, polyblasts and plasma cells) as shown in figure 1 *b*, but in no instance is a grouping of lymphoid cells

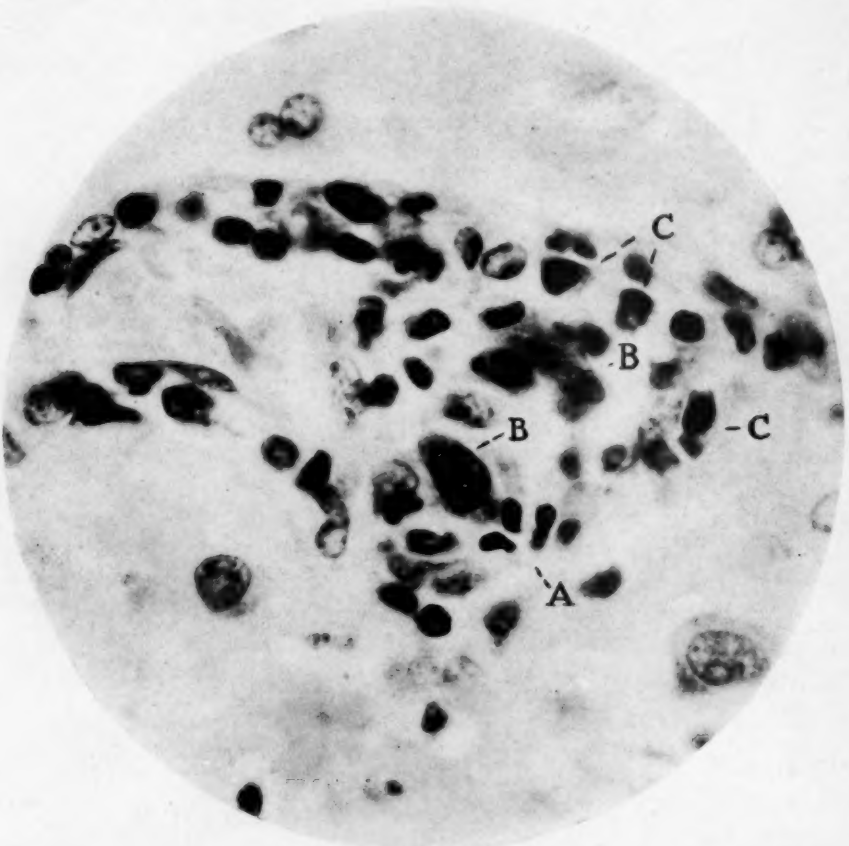

Fig. 9.—Capillary infiltration in chronic parenchymatous syphilitic encephalitis; *a* is an emigrating small lymphocyte, *b* a detached endothelial cell and *c* a plasma cell; × 1,000.

in the form of "Taches laiteuses" observed, as seen in poliencephalitis. A streamlike orientation and a migration of lymphoid cells away from the vessels is seldom, if ever, encountered, which explains the nonlymphoid aspect of the parenchyma in this disease (fig. 1). If the latter contains isolated, free, wandering lymphocytes, polyblasts or plasma cells, it owes their presence to single escapes, mostly from nearby capillaries. It may therefore be said that in paresis, with few exceptions, the exudate cells retain their perivascular habitat.

Glia.—In initial infiltrations, the glia cells frequently line up in a serial fashion parallel to the capillary, as though attempting to wall off the invading mesodermal derivatives. In the larger infiltrations, rod cells are frequently seen fulfilling the same function (fig. 7 *f*).

Endothelium.—Hypertrophy of vascular endothelium and a widespread proliferation of blood vessels of the capillary type is marked. Beginning frequently with a single, at times extremely elongated, sprout budded off from a capillary

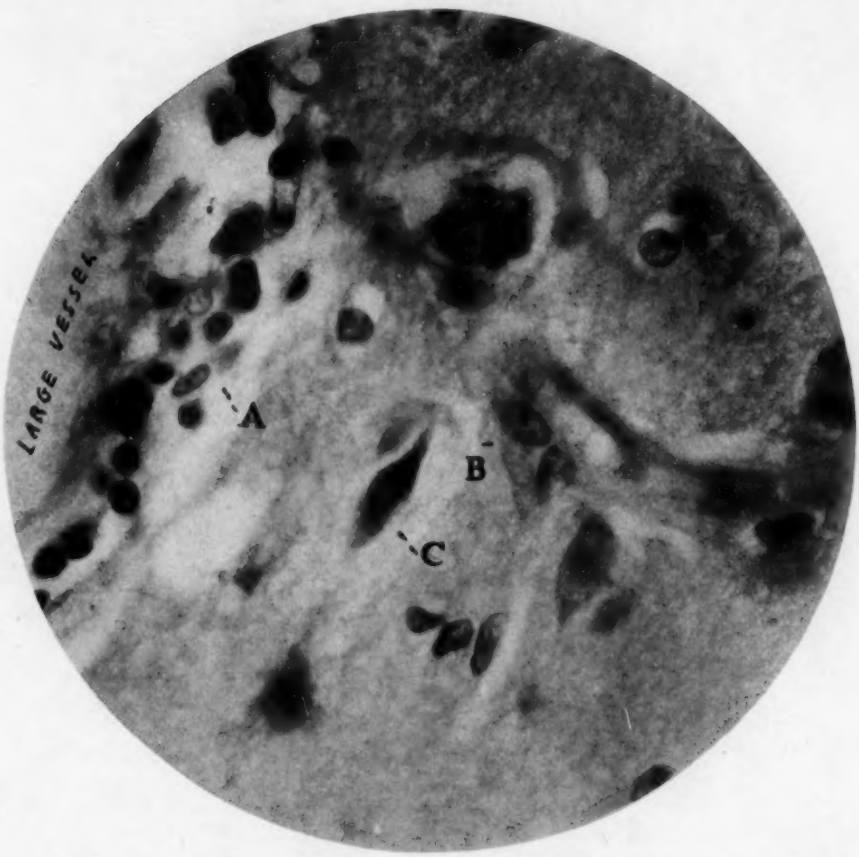

Fig. 10.—A budding capillary; *a* is a detached endothelial cell, *b* a branched capillary and *c* a detached endothelial cell; × 900.

structure, the endothelial tube grows into the parenchyma, and undergoes further branching (fig. 10 *b*), in this way giving rise in some instances to a remarkably close meshed network of capillaries. At times, the new capillaries assume a location parallel to the parental vessels, and when they are numerous in this vicinity they give the adventitial coat of the parental vessel a honeycomb appearance. A single capillary endothelial cell or a group of such cells frequently give rise to an abortive, nonfunctioning type of capillary, thereby leaving a variable number of endothelial cells free in the parenchyma (fig. 6).

Meninges.—The alterations in the pia-arachnoid are marked. These consist in a decided hypertrophy of the connective tissue elements, perivascular infiltration and emigration of lymphoid cells, differentiation of lymphocytes into plasma cells and an occurrence of mast cells. Since this study is strictly limited to a consideration of the perivascular infiltrations as they occur in the parenchyma of the central nervous system, a detailed description of the pial changes is omitted.

Comment.—A most appropriate opportunity is therefore at hand to ascertain any possible hemohistiopoietic activity on the part of the activated endothelium. Yet, in spite of the innumerable endothelial sprouts and newly formed capillary tubes there is no evidence of a single instance in which the endothelial cells give rise to any free mononucleate exudate cells either by mitotic proliferation or by rounding up. The differences between the infiltrating elements and the endothelial cells is illustrated by the fact that while some endothelial cells in forming new capillary sprouts may become detached from the strain of endothelium that is departing from the parent vessel (fig. 10 *b* and figs. 4 and 5), they never transform into free plasma cells, polyblasts or so-called "endothelial leukocytes," but retain either their characteristic endothelial cell morphology (fig. 4 *c*) or become changed into fibroblast-like structures with typical angular cytoplasmic processes (figs. 4 *d* and 9 *b*). A transitional stage in this transformation of the endothelial cells, characterized by the initial and marked angular broadening of the protoplasm (fig. 4 *d*), is frequently seen about the abortive types of newly formed capillary sprouts. It is also met in the larger infiltrations (fig. 10 *a*). Hence, many of the stellate fibroblast-like structures appearing as isolated constituents of the infiltration (figs. 2 and 7) may be interpreted as detached endothelial cells that have assumed a fibroblast-like form, for the most part indistinguishable from that of the local syncytially arranged fibroblasts. Thus, all of the material investigated in this case leads to but one conclusion, viz., that the endothelium is in no way instrumental in the production of mononucleate exudate cells.

Von Möllendorff's contention that under inflammatory conditions the local fibroblasts, through amitotic proliferation and a rounding up, give rise to a variety of free cells (histiocytes, polyblasts, granulocytes) may be seriously questioned. Such a process apparently does not take place in general paresis. In not a single instance do the perivascular connective tissue cells or the so-called adventitial cells of Marchand (small, spindle-shaped, clasmatocyte-like structures skirting vessel walls) show the alleged amitosis or rounding up. Therefore, it seems justifiable to assume that, in paresis as in poliencephalitis and acute epidemic encephalitis, the vast majority of the exudate cells represent emigrated lymphocytes and monocytes, with a small number of homoplastic derivatives of preexistent or previously extravasated lymphoid cells.

Since polymorphonuclears (eosinophils, neutrophils) are extremely sparse, they apparently do not, as a cell group, take part in the inflammatory process. Mast cells, however, participate in the process to a considerable extent, for plasmamast cells are found frequently as isolated elements, and histogenous mast cells are often seen among the connective tissue elements of the larger vessels. Preparations of the dura mater with attached fragments of periosteal tissue show large aggregations of mast cells, usually of the histogenous type.

Extravasation of red corpuscles of such frequent occurrence as is found in poliencephalitis and epidemic encephalitis is not noted, only a few isolated red corpuscles being present among the infiltrating cells.

Though specific stains were not employed, the hematologic technic used disclosed a decided increase of the collagenous fibers in the larger blood vessels, many of which showed progressive and regressive changes as originally outlined by Alzheimer.[37]

CASE 2. CHRONIC PARENCHYMATOUS SYPHILITIC ENCEPHALITIS (PARESIS)

The striking and rather uncommon feature in chronic parenchymatous syphilitic encephalitis is the widespread and in places extensive hyalinization in the cortex, causing marked alteration in the parenchymal architecture (fig. 11).[38]

The hyalinization spares the molecular layer and ceases abruptly at the base of the polymorphous layer. None of it is noted in the subcortex (white matter of the brain). Whenever it occurs, notably in the region of the large pyramidal cells, it involves the cellular elements, as well as the blood vessels. It disrupts the neuroglial supporting tissue into innumerable deep-staining, ragged clumps. At times, it assumes the form of massive, homogeneous structureless deposits, which replace all the normal cellular structures. These masses often acquire a mosaic-like distribution of small, irregular, light-refracting, hyalinized solid blocks (fig. 11 *a*). As a rule, glia nuclei with fragments of cell protoplasm are engulfed in the hyalinized mass, lodged in small spaces, giving the appearance of being enclosed in capsules.

The hyalinization in the blood vessels affects selectively the capillary type. Under low power, field after field shows many capillaries completely or partially hyalinized. About larger vessels, hyalinized material frequently forms collar-like masses intimately hugging the vessel wall. Constituents of the latter, especially the collagenous fibers, also undergo hyalinization. The intima of vessels so affected often splits into a series of homogeneous superimposed loops, between which there are arrested migrating cells. Frequently, the entire vessel shrinks into a solid, structureless mass, with the cellular elements either displaced to the periphery or encased in the hyalinized mass. In the latter location, the cells are frequently enclosed in a cavity of lacuna not unlike that seen in cartilage. Long stretches of small patent cylinders are met alongside of completely solidified capillary walls, which present a pattern not unlike that observed in mesenchymal bone formation and the linear marginal seriation of the osteoblasts characteristic of the latter is here simulated by the exudate cells, one or two rows of which are irregularly enmeshed or embedded in the vessel wall. Occasionally, the hyalinizing process causes a partial or complete degeneration of the enclosed cells. The latter show distortion and vacuolization of the protoplasm and pyknosis of the nuclei; however, more often, the cells retain a relatively normal morphology.

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37. In giving the histologic observations in the cases of general paresis to follow, emphasis will be laid on important differences rather than on details already described.

38. In a recent paper, K. Löwenberg (Ueber hyaline Degeneration der Grosshirnrinde bei Progressiver Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:1, 1924) described cases of general paresis with a similar extensive hyalinization of the cortical parenchyma and blood vessels. With the aid of chemical tests, he concluded that the structure is not amyloid, and is not related to fat or calcium deposits. The phenomenon, in his opinion, is essentially the result of changed nutritional conditions, the hyalinization of the vessels (especially of the media) being primary, the alterations in the parenchyma secondary.

Nonhyalinized vessels, many of which are present, often attain a maximal infiltration of from four to five rows. The cells here are predominantly lymphocytes, but plasma cells and macrophages are also present in varying proportions. Isolated mast cells occur about as frequently as in case 1.

In direct proximity to the vessels, as well as in the more remote extravascular territory, Russell bodies are observed. They are usually found in groups of from ten to fifteen, collected into a spherical mass. They are also found in the plasma cells, but decidedly less frequently than in these cells in case 1.

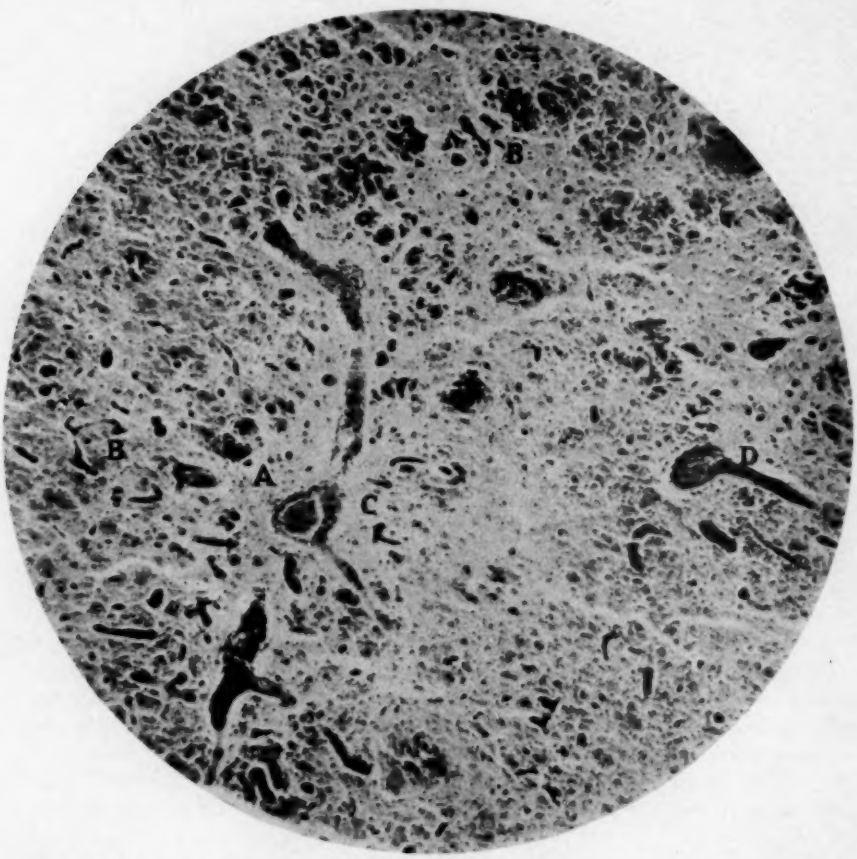

Fig. 11 (case 2).—Generalized hyalinization of capillaries in the cortex with a similar process in the parenchyma (black dots); × 65. The letter *a* indicates mosaic-like hyalinized solid blocks, *b* a hyalinized capillary, *c* an area of infiltration and *d* a hyalinized vessel.

In the hyalinized walls of many vessels are seen lymphocytes presenting the form of emigrating cells (fig. 12). It seems probable that the hyalinizing process, setting in before the cells had time to reach an extravascular habitat, have arrested their progress and encased them in the inert, homogeneous substance. If this view is correct, it may be assumed that one is dealing here with a "fossilized" emigrating lymphoid cell. It may be regarded as additional evidence in favor of

our contention that the majority of the exudate cells are hemic in origin. In our previous paper, we stated that the emigration of hemic cells is at times slow and arduous, because the cells frequently become lodged or compressed between the endothelial cells through which they are seeking passage. The effect of the hyalinization in this case offers additional evidence of the correctness of this view.

The hemic monocytes often assume a bizarre shape in emigration. This is particularly true around nonhyalinized vessels in zones of relatively normal parenchyma. The pictures of emigration in this case are somewhat less numerous than in case 1.

Though new formation of capillaries especially in the cortical layers is extensive, not in a single instance does the endothelium or local perivascular connective tissue give rise to free wandering cells of the polyblast type. Detachment of endothelial cells from the vessel wall with subsequent transformation into fibroblast-

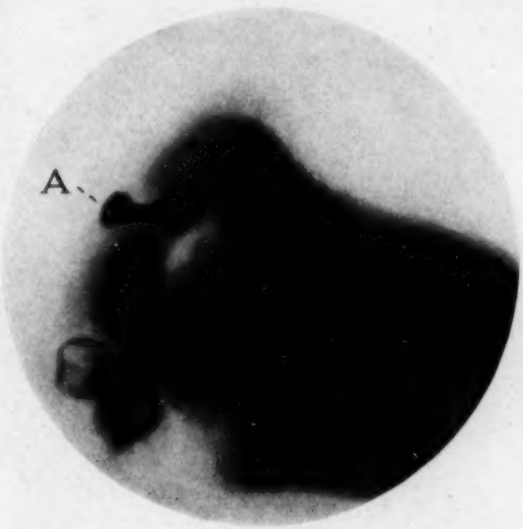

Fig. 12.—An emigrating large mononuclear (*a*) encapsulated in the hyalinizing mass; × 2,000.

like elements is less frequent here than in case 1. This is probably due to the hyalinization of many of the vessels.

Spinal Cord.—Sections of the cord show a widespread new formation of capillaries, especially in the gray substance. These rarely show infiltrations.

Meninges.—The pia is characterized by a perivascular infiltration much more pronounced than in the previous case.

CASE 3. CHRONIC DIFFUSE PARENCHYMATOUS SYPHILITIC ENCEPHALITIS

An outstanding feature of the condition represented in this case is the widespread and highly branched type of neocapillary formation (fig. 13). Perivascular infiltrations are decidedly less extensive here than in cases 1 and 2, with many vessels, though markedly altered, showing practically no exudates. The infiltrations about the capillaries consist, as a rule, of a single broken row of plasma cells

and lymphocytes in various stages of transition. The same is true of the infiltrations that reach the depth of from four to six rows about some of the larger vessels.

Peculiar to this case is the relatively high percentage of macrophages, which are nearly the only type of cell about some vessels while small lymphocytes predominate about other vessels, and about still others, notably the precapillary venules, plasma cells of oblong spindle contour are particularly numerous. Mast cells and plasma cells containing Russell bodies are extremely sparse here. Rod

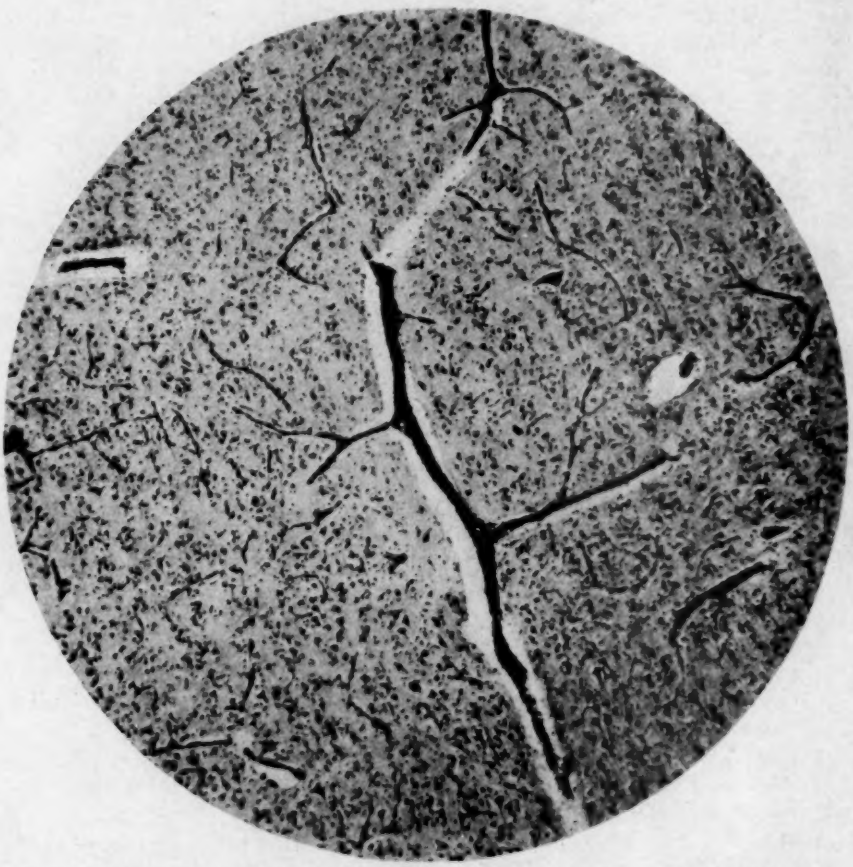

Fig. 13 (case 3).—The highly branched arborial form of new capillaries in chronic diffuse parenchymatous syphilitic encephalitis; × 65.

cells, on the other hand, are especially numerous. Extravasation of red corpuscles is in some places as pronounced as in poliencephalitis.

Aside from many detached endothelial cells which assume a fibroblast aspect, the vascular and capillary endothelium here again shows no evidence of producing free mononuclear phagocytic cells. This is particularly true of vessels about which macrophages constitute the major portion of the exudates, and also of the local vascular connective tissue elements. On the other hand, lymphocytes and

monocytes are frequently seen in transit through the vessel wall, warranting the conclusion that in this case as in the two previous instances the vast majority of the mononucleate exudate cells are hemic in origin.

CASE 4. MENINGOVASCULAR SYPHILIS CEREBRI

This case shows an unusually wide distribution and a massive type of perivascular infiltration. In the midbrain and especially in the pons, some of the

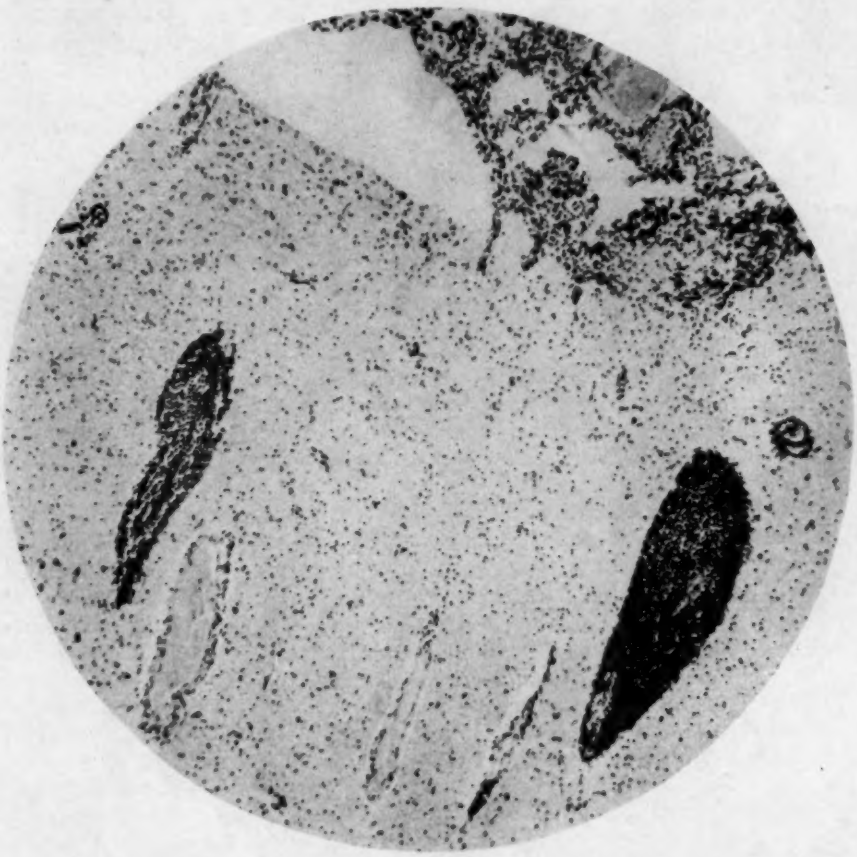

Fig. 14 (case 4).—Meningovascular syphilis cerebri. The infiltration is restricted to the space of Virchow-Robin. The pia-arachnoid is thickened and thickly infiltrated; × 80.

larger vessels show infiltrations from twenty to twenty-five cell rows in depth. The cells are so closely grouped as to give the perivascular area a block-pavement aspect (fig. 14). The vast majority of the infiltrating cells are small and medium-sized lymphocytes. Plasma cells, with intergrades from the lymphocytic types, are far less numerous than in the cases of paresis. The infiltrations often attain depths as great or even greater than those seen in poliencephalitis, but in no instance do they show the migratory, centrifugal orientation from the vessel wall

that is shown in encephalitis. They are strikingly restricted to the adventitial habitat and this very likely accounts for the nonlymphoid aspect of the parenchyma, which, aside from a widespread new formation of capillaries, is relatively free from mesodermal elements. However, in a few locations, exudates are found extending considerable distances from the vessel wall; in such instances, the infiltrating elements represent pial derivatives invading the interior of the brain. The pial alterations with the massive infiltration by lymphocytes and plasma cells often obliterate the boundaries between meninges and nervous tissue, the advancing lymphoid mass repeatedly carrying into the interior of the brain large and heavily infiltrated vessels, which may be traced back to an equally infiltrated parental vessel in the pia. Owing to this diffuse and advancing marginal infiltration, the neuroglia tissue in such affected regions reacts with considerable activation and mobilization, often giving rise to a linear arrangement of the glia cells against the vessel wall and a formation of compound granular cells with similar perivascular orientation.

The more deeply situated and larger vessels show infiltrations averaging from four to five rows in depth, while capillaries and postcapillary venules exhibit from one to two rows of exudate cells predominantly lymphocytes, many of which show mitotic proliferation. Large mononuclears are present in varying proportions. Mast cells are extremely sparse; polymorphonuclears are nearly entirely lacking, and eosinophils are only occasionally found.

In the more extensive infiltrations there are innumerable instances of lymphocytes and large mononuclears passing through the vessel wall. Occasionally, extravasation of lymphoid cells seems to have been accomplished through definite breaks in the endothelial lining, shown by the large quantity of red cells located in the adventitial spaces and the adjoining parenchymal tissue about such vessels.

There is marked hypertrophy of the endothelial cells and an extensive new formation and budding of capillaries. The endothelium, however, is apparently not concerned with the production of large mononuclear exudate cells or the so-called endothelial leukocytes.

Sloughing off of endothelial cells is a more common occurrence here than in general paresis. The completely detached structures either retain the characteristic endothelial morphology or became transformed into fibroblast-like elements, but never into free wandering phagocytic polyblasts (fig. 15). This is particularly true of the abortive type of capillaries in which the apparently separated endothelial cells have full opportunity for a display of a possible latent cytopoietic tendency. Even here, the detached cells are never seen to round up, but acquire a characteristic irregularity of the cell body, with an oblong or oval nucleus, which is poor in chromatin content, thus becoming indistinguishable from fibroblasts.

In areas somewhat remote from blood vessels or in zones totally devoid of vascular constituents are strands of cells arranged in cords or in tubes, the nature of which is not clear (fig. 16). An endothelial origin for them was claimed by Dunlap in a recent paper on encephalitis, in which there are photomicrographs of similar structures. In our material, these cells are not seen rounding up or phagocytosing foreign material, as it was claimed by him that they did in his cases. Since occasionally these strands can be traced to the ependymal lining, they might be regarded as derivatives of ependyma invading the parenchyma.

CASE 5. MENINGOVASCULAR SYPHILIS CEREBRI

The perivascular infiltrations in this case are of a decidely less pronounced character than in case 4, with the exception of areas of softening, in which they are extensive.

The pia-arachnoid membrane covering the areas of softening is a thickened mass of lymphoid cells composed mainly of densely packed lymphocytes and plasma cells, among which there are many eosinophil leukocytes. Beneath this lining, the area of softening extends inward to a great depth over the entire cortex (fig. 17).

In the area of softening there is an intensive activation and mobilization of the glia elements with the formation of free compound granular cells, which in places take the character of solid masses. The walls of the larger blood vessels show

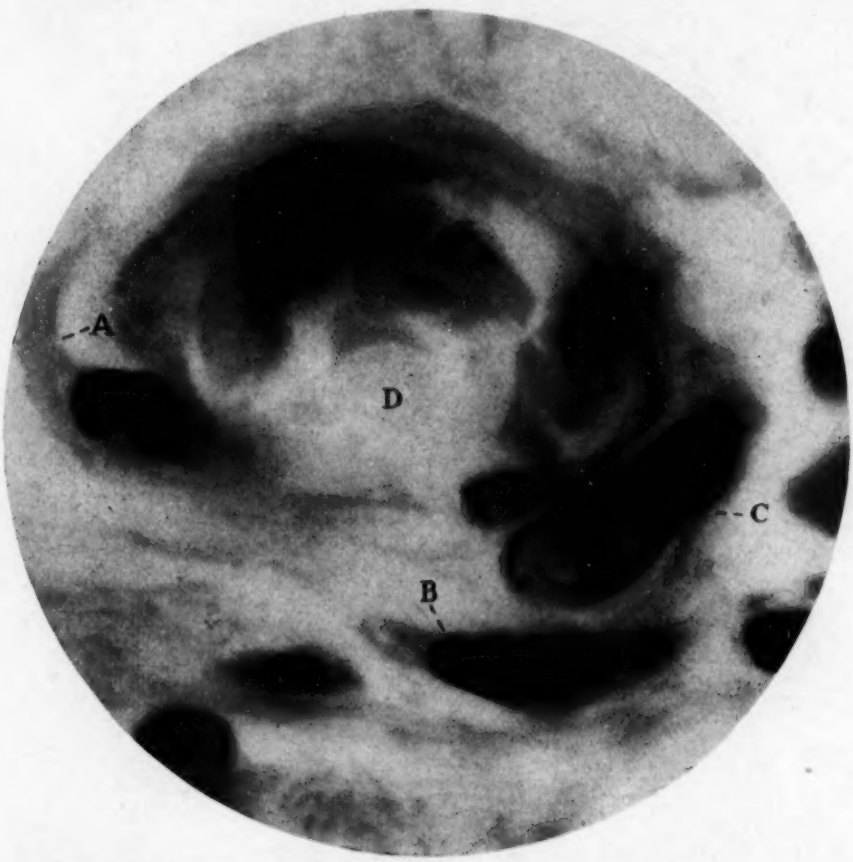

Fig. 15.—Detachment of endothelial cells; *a* indicates an initial loosening of an endothelial cell, *b* an endothelial cell retaining its normal morphology and *c* an endothelial cell undergoing transformation into a fibroblast-like structure. The lumen of the blood vessel is indicated by *d*; × 3,000.

a varying quantity of exudate cells, predominantly lymphocytes and plasma cells. Both types of cells are frequently encountered in the extravascular territory, but, as a rule, the majority of these cells on extravasation either undergo degeneration or differentiation into compound granular cells. This is seen in the many transitional stages of lymphocytes. The process is essentially the same as that described in our previous paper on poliencephalitis, with this difference, that frequently and

especially in the newly formed capillary the hemic lymphoid cells accomplish their transformation while they are still in transit through the vessel wall or immediately thereafter. The sparsity of plasma cells in the midst of exudate cells in the extravascular territory in the area of softening may be accounted for by the rapid differentiation of the infiltrating elements into compound granular cells; typical transitional stages are not an infrequent occurrence.

Eosinophil leukocytes are in places so numerous that these places simulate fields of focal eosinophilia. Both the gitter cells and the large mononuclears

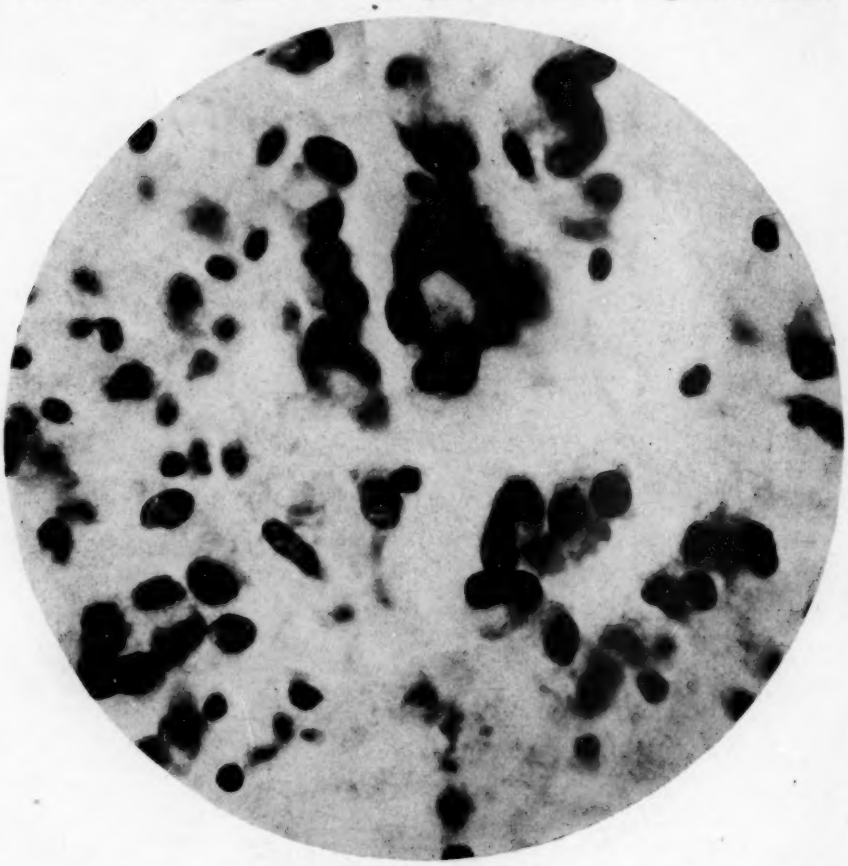

Fig. 16.—Cords and tubes of ependymal cells (it is not likely that these are endothelial cells); × 900.

exhibit phagocytic tendencies, the engulfed material being, prevailingly, broken red corpuscles.

The zone characterized by a marked formation of new capillaries, capillary sprouts and venules ends repeatedly in a frayed out, loose aggregation of syncytially arranged cells. In close proximity to the latter there are large isolated cells with long cytoplasmic spiny processes and lightly staining nuclei, obviously instances of recently sloughed off endothelial cells. The same process may be observed in the larger vessels, demonstrating, as in no other case, the recession of endothelial cells with a subsequent transformation into fibroblast-like structures.

In the vicinity of degenerated vessels, the endothelial cells are apparently the last to become metamorphosed. The detached endothelial cells (fig. 18) either retain a characteristic endothelial-fibroblastic aspect (*a*) or become transformed into large, polymorphous, at times multinucleate structures the protoplasm of which has a ragged appearance with many long spinelike processes (*b*). None of such cells are seen differentiating into elements of the large mononuclear type. In the deeper zones of the softened cortex there is a relatively rarefied region consisting almost exclusively of compound granular cells.

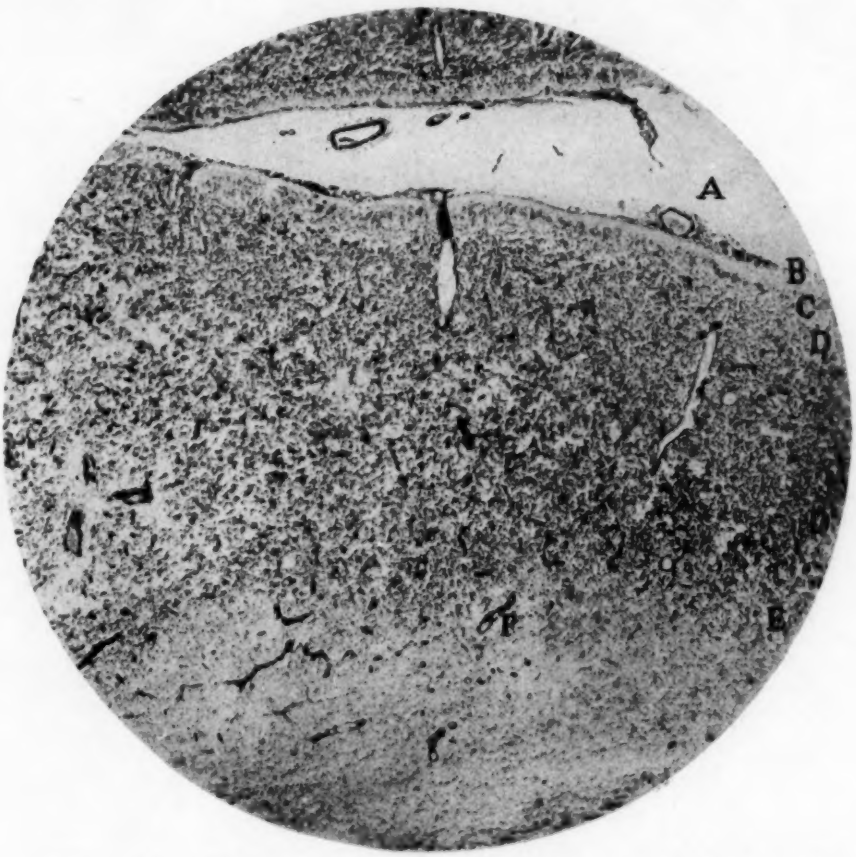

Fig. 17 (case 5).—An area of softening (from 2 to 3 mm. in depth). The letter *a* indicates the pia-arachnoid membrane, *b* the molecular layer, *c* a highly vascular layer, rich in ameboid glia cells, *d* a zone densely populated by lymphoid cells that have emigrated from the enclosed vessels, *e* degenerating blood vessels and *f* a degenerating new-formed capillary; × 28.

In the same zone there are many degenerating capillaries showing exudates undergoing transformation into gitter cells (fig. 17 *e*). Beyond this zone there is the border line of the invading softening process. Here the neuroglia present a wide-mesh syncytial arrangement, many of the glia cells showing active ameboid movement, others presenting the various stages of a differentiation into compound

granular cells. With few exceptions, practically all vessels located in this zone are in a state of degeneration. The perivascular infiltrations are represented predominantly by lymphocytes, few of which are normal.

There are extensive extravasations of red cells, which are usually lodged in the adventitial spaces. Still more inward there are many closely grouped newly formed capillaries with initial infiltrations (fig. 17 *f*).

The softening area is particularly interesting from the standpoint of emigrating lymphocytes and monocytes. Active emigration is observed in the vessels in this

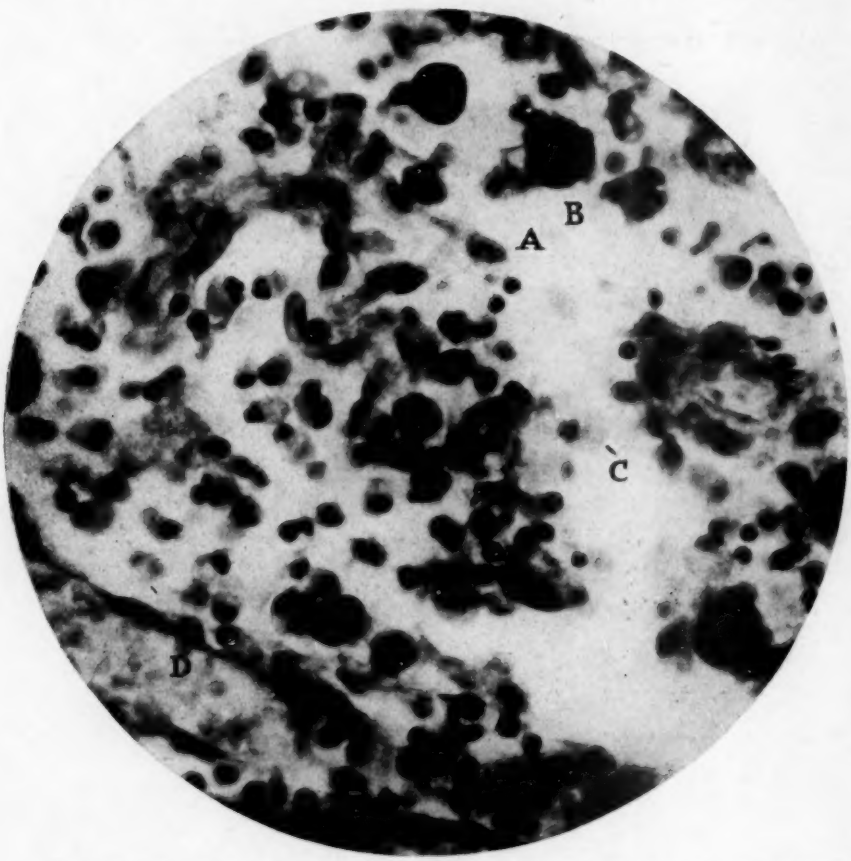

Fig. 18.—Change in zone *d* of figure 17, showing the breaking up of blood vessels, loosened endothelial cells (*a* and *b*) and gitter cells (*c*). The letter *d* indicates a blood vessel; × 600.

region. Emigrating eosinophil leukocytes are also seen; those in transit through the vessel wall present the same contortions of nucleus and cytoplasm as do the lymphoid cells (fig. 24).

An extensive formation of new capillaries and a rebudding of the latter is also seen in the parenchymatous areas other than that undergoing softening. Groups of neocapillaries are also found in the adventitial tissue of some of the larger vessels (fig. 19) in which as many as ten such structures may be counted.

In extravascular territory, the capillaries show either no exudate or few of them. On the other hand, a few of the capillaries exhibit an initial hyalinization characterized by the homogeneous, metachromatic occlusion of the lumen. Here, as in case 2, emigrating cells in isolated places are encountered showing a complete encapsulation in the hyalinized matrix. Formation of the latter is seemingly restricted to capillary regions for in postcapillary venules and in larger vessels it is never noted.

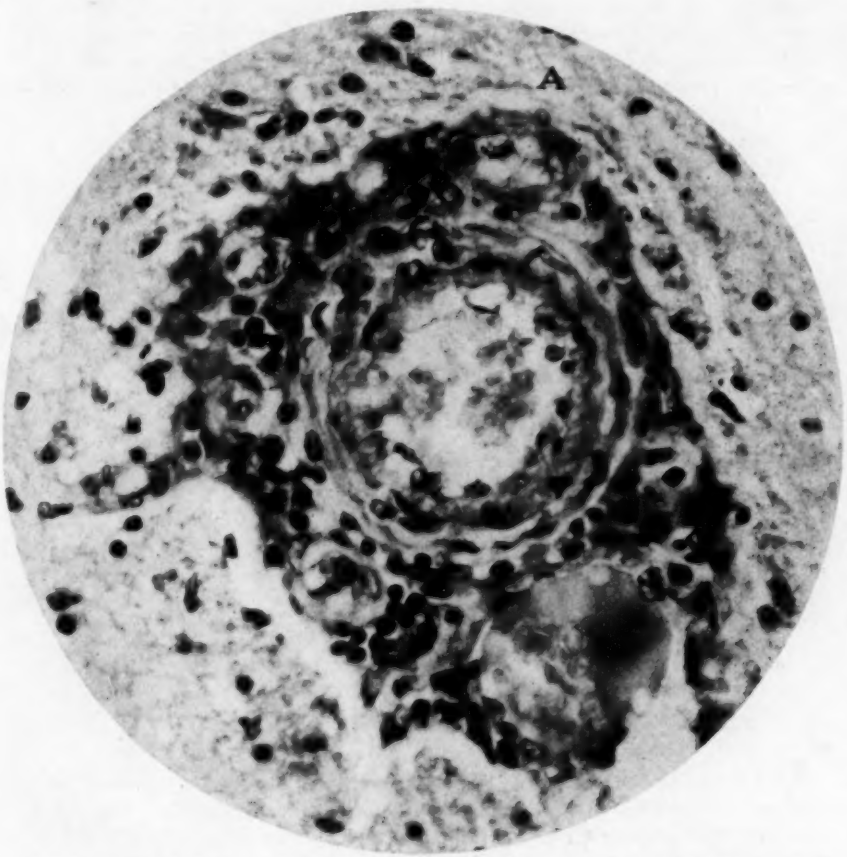

Fig. 19.—A large vessel with radially disposed new-formed capillaries; *a* indicates one of these; × 500.

Though not as frequent as in regions of softening, the emigration encountered in other localities is nevertheless typical (fig. 20).

A sloughing off of endothelial cells with a subsequent recession from the vessel wall and the assumption of a fibroblast morphology is often noted. Aside from this, the endothelium and its adjoining perithelial connective tissue is in all instances cytogenically inactive.

CASE 6. MENINGOVASCULAR SYPHILIS CEREBRI

This case, unlike case 5, contains no areas of softening; still, the pial disturbances are extensive. Massive lymphocytic collections show streamlike fur-

rows of extravasated red cells (hemorrhages). In other areas, polymorphonuclear leukocytes predominate. The larger vessels are often densely muffed with lymphocytes and plasma cells and, in addition, exhibit a well advanced hyalinization.

In spite of this vast pial disturbance, the boundary line between the cortex and the meninges remains for the most part distinct. At intervals, it is broken by a massive invasion of polymorphonuclear and mononuclear elements, with lymphocytes, polyblasts, plasma cells and a varying quantity of fibroblasts.

The marginal zone of the cortex contains numerous migrating lymphocytes, polyblasts and plasma cells in various stages of differentiation. There is no extensive neoformation of capillaries with initial infiltration as noted in case 5.

As a rule, perivascular infiltration is restricted to vessels close to their points of origin from the parental vessels in the pia. They begin there with an infiltra-

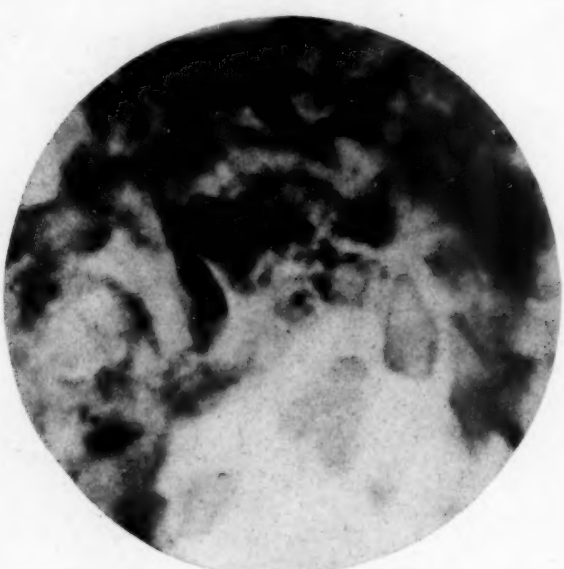

Fig. 20.—A large mononuclear in transit through a vessel wall; × 2,000.

tion of from four to six rows, but as they proceed into the cortex, they show a progressive diminution of the exudates. The perivascular elements here are predominantly lymphocytes, many of which show hypertrophy and mitotic division; occasionally, plasma cells in various stages of differentiation outnumber the lymphocytes. Large mononuclears are relatively sparse; eosinophil leukocytes and mast cells are entirely lacking or extremely rare.

The endothelium, aside from showing detachment of individual cells that frequently become indistinguishable from adjacent fibroblasts, is inactive.

The parenchyma of the subcortex is decidedly nonlymphoid, save for a few foci of infiltration, which in the midst of the highly ameboid glia cells show a varying quantity of migrating lymphocytes, histiocytes and polyblasts. The perivascular infiltration is slight. In maximal proportion, it reaches from three to four rows in some of the larger vessels, averages from one to two rows in many others and about capillaries is, for the most part, entirely lacking.

The lumen of some of the vessels with macrophages as the dominating infiltrate is densely populated with large pigmented mononuclears. The extravasation of

red cells occasionally met about capillaries assumes marked proportions in the adventitial spaces of a few of the larger vessels.

New formation of capillaries is rather generalized but is not as pronounced as in the previous case. A less marked form of hyalinization is noted in some of the capillaries; it offers an opportunity for an establishment of what we propose to call "fossilized emigrating lymphocytes," i. e., cells embedded in the hyaline matrix while in transit through the vessel wall, two of which are shown in figure 21.

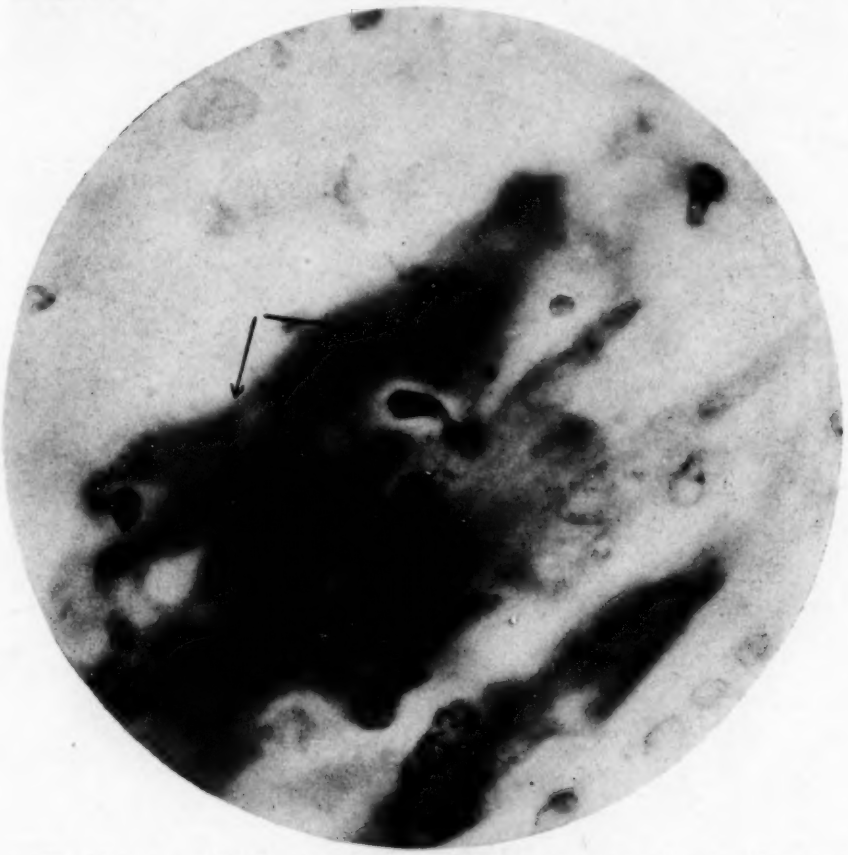

Fig. 21.—A hyalinizing blood vessel showing two emigrating lymphocytes encapsulated in the hyalinized matrix, "fossilized emigrating lymphocytes."

CASE 7. VASCULAR SYPHILIS CEREBRI

This case differs from the two that have been described in presenting relatively normal meninges. Neither infiltrating elements nor an unusual thickening is noted. The parenchyma of the brain shows a unique type of vascular lesion not seen in either encephalitis or in the various cases of cerebral syphilis described. Nearly all the larger vessels show hyperplasia of all their layers, notably of the intima. With few exceptions, such vessels show broad adventitial coats, the fixed cells of which fray out extensively into a mesenchyma-like, syncytially arranged connective

tissue network, the meshes of which are conspicuously numerous and widened. Here, in addition to the many newly formed capillaries, distinct small arteries and veins may be seen with thickened intima.

The infiltration about such vessels is nearly exclusively restricted to the adventitial coat and is composed mainly of scattered small lymphocytes, many of which have deep staining and at times decidedly pyknotic nuclei. This and the fact that plasma cells are conspicuously absent and macrophages and large mononuclears only occasionally met seemed to indicate that the infiltration had been arrested

Fig. 22.—The bizarre shape assumed by a large mononuclear in the process of emigration; × 2,000.

in its early stages. The total lack of mitotic figures in the lymphoid exudates, the extreme sparsity of active emigrations and the nonhypertrophied and in instances pyknotic condition of the vascular and neocapillary endothelium lend additional evidence to this view.

In regions in which the neuroglia tissue has become extremely rarefied, regressive changes in the larger vessels are still more pronounced. Here the exudates are extremely sparse. The adventitial coat consists of a disorganized mass of loosely concerted connective tissue cells, many of which show signs of degeneration, a process equally notable in the disintegrating local neocapillaries. In such

vessels, little is left of the media and the intima save a distorted convoluted cellular mass, in the midst of which most prominent is the corrugated elastic membrane.

This case presents a third type of vessel, which in cross-sections simulates a large lymphatic. These vessels are composed nearly exclusively of endothelial cells, relatively few of which are normal. About such structures, exudates are, as a rule, entirely lacking; when present, they exhibit marked degeneration. These vessels are undoubtedly instances of newly formed capillaries, which subsequently have assumed giant proportions.

Fig. 23.—The dumb-bell shape of a large mononuclear in transit through the vessel wall; × 2,000.

Finally, an infiltration of closely grouped cells approximating in type that in the previous cases is met with in some of the small veins and postcapillary venules. Here the exudates, while predominantly composed of small and, for the most part, normal appearing lymphocytes, included plasma cells, large mononuclears and macrophages in varying proportions. A few active emigrations are encountered. Sloughed off endothelial cells with a retained irregularity of cytoplasmic contour are likewise encountered, a phenomenon not noted in the previously described vessels.

Occasionally, larger vessels running in from the periphery are accompanied by connective tissue septums, which at intervals are densely populated by long, spindle-shaped, clasmatocyte-like structures heavily laden with greenish pigment granules. The latter are found in local macrophages and in the fixed endothelium. In spite of this, however, no genetic relationship can be established between the pigmented free cells and the vascular endothelium. On all occasions, the endothelium, as well as the perithelial connective tissue, is cytogenically inactive in respect to a production of the so-called endothelial leukocytes or large mononucleate exudate cells.

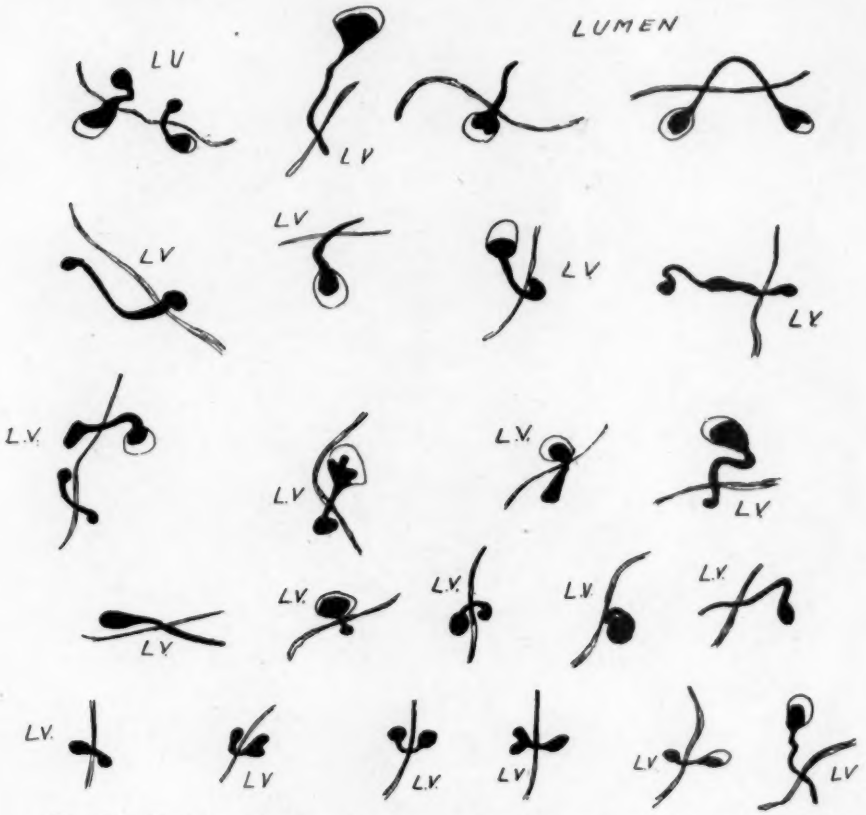

Fig. 24.—Various alterations in contour of nucleus and cytoplasm assumed by lymphoid cells during emigration: the upper three rows are large mononuclears; the lower two rows are small and medium-sized lymphocytes. *LV* designates the vessel.

All the figures were drawn with the camera lucida at a uniform magnification. Leitz apochromatic oil immersion 1/12 Fl. objective; compensatory oculars × 10.

SUMMARY

Beginning with the earliest investigations of Cohnheim and his contemporary Virchow, the nature, origin and significance of the so-called small round cell infiltration occurring in various inflammatory conditions have been the subject of repeated investigations and discussion. The

Fig. 25.—*A* shows an initial infiltration about a capillary, showing a plasmamast cell and two plasma cells; *B*, a typical plasma cell displaying the paranuclear clear area; *C*, a lymphocyte (*a*) and a large mononuclear (*b*) acquiring the character of macrophages, (*c*) an emigrating lymphocyte; *D*, an emigrating large mononuclear; *E*, Russell bodies simulating eosinophil granules enclosed in plasma cells.

literature claiming a histogenous origin for these cells, though decidedly more extensive than that arguing for a hemic origin, is, however, by no means equally conclusive.

Ranvier established the existence of a free wandering type of cell in the loose connective tissue (clasmatocytes) that under normal and pathologic conditions exhibits polyvalent hemohistiopoietic potencies. This was verified by subsequent workers, who variously named these structures resting wandering cells (Maximow), adventitial cells (Marchand), histiocytes (Kiyono) and hemohistioblasts (Ferrata). These cells were investigated from the point of view of embryogenesis and comparative histogenesis and were recognized in natural and experimentally produced inflammatory conditions. Their character was determined by intra vitam staining with various colloidal dye injections (Pyrrholblau, trypanblau, lithium-carmine), by growth of various tissues in vitro and by the supravital staining methods (neutral red, Janus green). It was then found that these variously named, dye-storing cells belong to the coherent organization that in current literature has definitely become recognized as the histiocytic apparatus or the reticulo-endothelial system.

It is now a well established fact that in the adult organism there are, in addition to the generalized resting wandering cells, fixed histiocytic elements that under normal and especially under pathologic conditions may mobilize, proliferate and round up to form free wandering phagocytic elements, including granulocytes. These fixed histiocytic cells constitute the reticular cells of the lymphoid and myeloid tissue, the cells lining the sinuses of the lymph nodes and the venous channels of the bone-marrow, spleen and liver (Kupffer cells) and possibly the cells lining the venous capillaries of the suprarenal glands and the hypophysis. It is this group of cells only that is correctly covered by the term reticulo-endothelium. In this restricted sense, the term is particularly appropriate, reticular implying the histologic character of the riporinal cells; endothelium their function in establishing channels for the lymph and the blood stream through the respective organs.

No sooner had Goldman,[39] Tschaschin,[40] Aschoff and Kiyono,[41] Kiyono [42] and others established the morphology and cytopoietic signifi-

39. Goldman, E. F.: I. Die äussere und innere Sekretion des gesunden und kranken Organisms im Lichte der vitalen Färhung, Beitr. z. klin. Chir. **64**:192, 1909; II. **78**:1, 1912.

40. Tschaschin, S.: Ueber die ruhenden Wanderzellen und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphocyten, Folia haemat. **17**:317, 1913.

41. Aschoff, L., and Kiyono, K.: Zur Frage der grossen Mononukleären, Folia haemat. **15**:383, 1913.

42. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

cance of the reticulo-endothelial system than repeated attempts were made to include the generalized vascular endothelium (both deep seated and peripheral) as actively participating in the production of the free wandering phagocytic cells. In the current literature, such vascular endothelial derivatives are spoken of as endothelial leukocytes (Mallory, 1914), large mononuclear phagocytes (McJunkin, 1925), endothelial phagocytes (Foot, 1925) and monocytoid elements (Di Guglielmo, 1926).

Pathologists, especially, are prone to adopt this view of a vascular endothelial origin of the large mononuclear to account for the frequent appearance of this type of cell in a variety of infectious diseases, such as malaria, endocarditis lenta, streptococcemia, tuberculosis, syphilis and various other types of chronic inflammatory lesions. This tendency may be traced to Patella (1903-1923), who regarded large mononuclears and the major portion of the lymphocytes as "cadaverously" isolated vascular endothelial cells. It was substantially influenced by Mallory (1898) with his repeated assertion (1914) of a vascular endothelial origin for the endothelial leukocytes, and is seemingly difficult to disestablish because of Marchand's (1898-1902) classical studies on the polyvalent cytopoietic potencies of the adventitial cells skirting the blood vessels. Influenced by the investigations of his pupil Herzog, Marchand in recent years (1921-1924) considered the adventitial cells as derivatives of the vascular endothelium, which, when in a free ameboid state, are capable of giving origin to many of the small elements appearing in inflammatory lesions.

Indeed, it is proved that endothelial components of the reticulo-endothelial system exhibit polyvalent hemohistiopoietic potencies under normal and especially abnormal conditions, but attempts to prove a similar potency for the generalized vascular endothelium have thus far been strikingly inconclusive. In spite of the numerous investigations made and the various methods employed (especially that of injections of india ink) the evidence to date has not been sufficient to justify the axiomatic conclusion that the generalized vascular endothelium gives origin in any notable quantity to macrophages, polyblasts, small and large mononuclears, histiocytes, epithelioid cells, dust cells, syncytial or giant cells, or any of the free wandering cells met in inflammatory reactions. The situation is admittedly different in respect to the reticulo-endothelial system, for here any of the aforementioned cells may differentiate from the local endothelium, which, to avoid an all too prevalent confusion, might be called the riporinal endothelium as contrasted with the vascular endothelium.

That even monocytes take their origin from the reticulo-endothelial system has repeatedly been asserted (Schilling, Schittenhelm and Erhardt, Masugi, Buengler and others). This view, disparaged by the

late Maximow, has recently been categorically denied by Bloom, who maintains that proof of such a transformation is lacking.

The present investigation, like the previous one on encephalitis, afforded ample opportunity for a detailed study of the cytopoietic powers of the vascular endothelium. The reactive phenomena of the latter were noted under a variety of conditions, such as hypertrophy, swelling, new formation of capillaries, disintegration of constituent cells, partial or total degeneration and breaks in vessel walls because of massive diapedesis, yet no instance was recorded of vascular endothelium participating in any way in the production of free wandering cells (large mononuclears, histiocytes, polyblasts, macrophages) either through mitotic proliferation, desquamation or otherwise.

In syphilitic lesions, endothelial cells frequently become sloughed off from the vessel wall, but such detached cells either retain their characteristic endothelial aspect or become transformed into fibroblast-like structures, which, when somewhat receded from the vessel wall, are frequently indistinguishable from adjoining perivascular fibroblasts. This observation is by no means new. Over a quarter of a century ago, Maximow recorded the phenomenon as occurring in inflammatory reactions and has subsequently rediscovered the process in variously treated tissue cultures.

Important recent corroboration of the desquamation is found in the observations of Clarke and Clarke (1927) in living capillaries of amphibian larvae. The detached endothelial cells, in their opinion, remain specific and are devoid of ameboid movement. The phenomenon, in their opinion, is due to a weakened condition of the animal or to some mechanical injury.

Jolly in his earliest works, by means of injections of silver nitrate into the peritoneal cavity, observed the similar phenomenon of a sloughing off of endothelial cells and observed that, on occasions, "les cellules endotheliales ont pris l'aspect de veritable cellules conjonctives" (the endothelial cells appeared like true connective tissue cells). Jolly (1923) differed with Maximow by asserting that while some of the endothelial cells are altered in this fashion a considerable quota of them become rounded up into spherical structures (macrophages, polyblasts).

For the most part, contemporary workers on endotheliopoiesis, Herzog, Marchand, Dunlap, Oeller, Töppich, Siegmund, Sabin, Doan and Cunningham, Di Guglielmo, Foot and others, failed to mention this recession from the vessel wall of endothelial cells that retain the endothelial morphology or assume a fibroblast-like appearance. Histogenically, the process should offer no difficulty, since embryologically the early endothelial cells represent modified mesenchymal cells; the occurrence of a reverse process under pathologic conditions in which endothelial cells assume a fibroblast-like morphology may readily be conceded.

In current contributions on the origin of the perivascular exudates, the vague statement is often made that they arise from the cells of the vessel wall or from the so-called "Gefässwandzellen." Since both expressions leave one in a quandary as to what type of cell is meant, their use should be discontinued, especially so since in the light of modern hematology a sufficient variety of terms is available to describe accurately the various types of cells that may be encountered in the vessel wall.

A step in this direction is taken by von Möllendorff, who in his recent work interpreted the adventitial cells not as independent specific entities but as attached constituents of the general fixed fibroblast-net. His views as to the polyvalent hemohistiopoietic potencies of the fibroblast need not be discussed at length here; it is only necessary to say that the specificity of the fibroblasts is so well established that a resuscitation of older theories assigning a developmental capacity to the cell will occasion only needless discussions.

Over twenty-five years ago, Maximow (1902) contributed his classical studies on the inflammatory reaction of the connective tissue elements, notably that of the fibroblasts. In this work, he showed that the fibroblasts had a specific spindle-shaped stellate form, that their only mode of proliferation was through mitosis, and that among the various other inflammatory cells they played a decidedly unimportant rôle. This view Maximow subsequently corroborated by observation on cultures of connective tissue; for here, in the living condition, fibroblasts likewise appeared as specifically established elements with no evidence of further progressive histogenetic powers. Finally, in his last studies [43] on explanted tissues, he was able to show that lymphocytes may develop into fibroblasts, which, once established, notably never lose their specific morphology but, in laying down typical connective tissue, assume the function of ordinary fibroblasts.

Identical results were obtained by Bloom (1928). Rabbit lymph cultures in vitro showed within from six to eight hours a differentiation of small and large lymphocytes into the typical dye-storing mononuclears and polyblasts of inflammation, some of which later changed into fibroblasts.

Ferrata and the Italian school also repeatedly held out for the specificity of the fibroblasts. Jolly, admitting a phagocytic activity for the cells, regarded their final differentiation as permanent. In our own material (that on which this paper is based, as well as that on which our previous publication on encephalitis was based), the fibroblasts failed to reveal any activity in the production of free wandering cells or granulocytes, as asserted by von Möllendorff. In all instances, even when the

43. Maximow, A.: Development of Nongranular Leucocytes (Lymphocytes and Monocytes) into Polyblasts (Macrophages) and Fibroblasts in Vitro, Proc. Soc. Exper. Biol. & Med. **24**:570, 1927.

perivascular infiltration was maximal, fibroblasts retained their stereotyped morphology and played a decidedly secondary rôle. When hypertrophied connective tissue was met with in its most extreme form, as for example in the semilunar ganglion in one of the cases described here, fibroblasts never exhibited the alleged amitosis as an accompanying process in the production of free cells (von Möllendorff). Binucleate fibroblasts were encountered, but these represented indentations and segmentations of nuclear material rather than direct cell divisions, for never was an interruption of protoplasmic wall or a rounding up of these cells noted. The mitotic figures were seen in fibroblasts. Those encountered seemed sufficiently typical to substantiate Maximow's recent statement that "the only conclusively demonstrated mode of proliferation of the fibroblasts is mitosis."

It is a peculiar coincidence that both here and abroad pathologists during the last twenty years have made repeated attempts to derive the large exudative mononuclears from the vascular endothelium rather than concede a direct hemic origin of the cell by way of emigration through the vessel wall. Many consider the small circulating lymphocyte a cell type as permanently differentiated as the erythrocyte (Ferrata). Hirschfeld [44] denied its power for progressive development in cultures of leukemic blood. Others, while admitting a diapedesis of lymphoid cells, deny or at least question the ability of these to develop into granulated elements or into polyblasts in inflammatory reactions, especially those of the acute type.

Opposed to this somewhat arbitrary stand, following the lead of the pioneers Metchnikoff, Cohnheim and especially Maximow, there is a formidable array of workers offering evidence not only of the possibility, but of the decided frequency of the emigration of lymphocytes and large mononuclears and their subsequent polyblastic differentiation. Maximow as early as 1902, in his studies on experimental aseptic inflammations, advanced his theory of a mixed origin of the exudates, maintaining that while a small quota represent derivatives of local pre-existent small wandering cells (emigrated lymphocytes) and clasmatocytes, the vast majority are to be interpreted as hemic lymphocytes that through emigration have attained a perivascular habitat, where a polyblastic differentiation of them frequently occurs. Maximow has, in the face of strong opposition, consistently held the same opinion in his works on purulent inflammations, on the ontogenesis of blood cells, on the nature of connective tissue and recently on the cultures of lymphoid tissue, normal and inoculated with tubercle bacilli.

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44. Hirschfeld, H.: Züchtungsversuche mit leukaemischem Blut, Folia haemat. **34**:39, 1927.

Jolly is as affirmative as was Maximow, maintaining that the major portion of the cells in inflammation is constituted of emigrated lymphocytes through diapedesis. This phenomenon of lymphoid cells passing through the cell wall has repeatedly been confirmed by various workers. A list given by Maximow in a recent review on mesenchymal reactions includes the names of Ziegler, Schwarz, Helly, Zieler, Verebély, Fischer, Homén, von Fieandt, Wallgren, Tschaschin, Bergel, Dantschakoff and Seidlein, Kraft, Stilwell, Lang and Alfejew. To this list should be added the recent work of Bloom (1928), who maintained that in subcutaneous abscesses of rabbits infected with *Bacillus monocytogenes* the exudate cells represent, exclusively, transformed emigrated lymphocytes and monocytes.

Our present studies on syphilitic lesions and those previously reported on encephalitis have revealed many instances of lymphocytes and large mononuclears (monocytes) passing through the endothelial wall in full corroboration of Maximow's and Jolly's original contentions.

In the process of emigration, lymphocytes and large mononuclears often show decided variations in their nuclear and cytoplasmic contours, but at times extravasation is accomplished with slight changes in cell area and morphology. Often both cytoplasm and nucleus are drawn out into long, irregular structures, the advancing portion of the cell containing the main mass of the cell contents. Small and medium-sized lymphocytes in transit through the capillary wall assume such a degree of basophilia as frequently to obscure all traces of cytoplasm. Hence dark, round masses with pronounced pseudopods ending in rotund fashion in juxtaposition or in contact with the endothelium are to be interpreted as emigrating lymphocytes and not as tangential sections of endothelial cells (Marcora[45]). Such transient lymphocytes can be seen in small capillary tubes showing perfect unbroken endothelium near which are to be found previously extravasated, migrating and dividing free cells.

Curved dumb-bell-shaped, deeply staining nuclei with clearcut cytoplasmic contours, seen frequently outside the vascular endothelium, are not desquamated endothelial cells, but recently emigrated lymphocytes or large mononuclears. Thin strands of nuclear material running from the capillary lumen to a main cell body located in the third or fifth row of lymphocytes indicate clearly that the emigration is at times slow and arduous.

After extravasation, the behavior of the lymphoid cells varies. Hypertrophy is common for all the lymphocytes. Many of the latter, together with the large mononuclears, change into polyblasts,

45. Marcora, F.: Sull' origine delle infiltrazioni perivasali nella encefalomielite epidemica, Haematologica **2**:323, 1921.

macrophages, histiocytes and plasma cells, with the differentiation into plasma cells being of far greater frequency in the lesions of syphilis than in those of poliencephalitis or acute epidemic encephalitis.

The streamlike orientation and migration of lymphoid cells in the vicinity of blood vessels so frequently noted in encephalitis gives additional evidence of a hemic origin of the cells. In the present material, this phenomenon of migrating away from the adventitial spaces was not noted, which is characteristic for infiltrations in syphilis cerebri.

To meet the question whether the active emigration does not represent superimposed cells, it may be said that this could not be the case; for all the photomicrographs portraying emigrating cells were taken with high aperture lenses and critical illumination, so that only a single plane was in focus at one time. In every instance, it was possible to choose a plane either above or below that of the depicted emigrating lymphocyte, and the conclusion seems obvious that the cell in question represented an individual lodged between the endothelial cells, through which it was seeking passage to a perivascular habitat.

CONCLUSIONS

In all types of syphilitic lesions, the vast majority of the infiltration elements in the adventitial spaces is constituted of emigrated lymphocytes and monocytes, as evidenced by the numerous emigration pictures seen, with a small quota of homoplastic differentiation products of preexistent or previously extravasated lymphoid cells.

As a rule, the perivascular infiltrations in the various types of syphilis are decidedly less marked than in poliencephalitis or in acute epidemic encephalitis. In one case, however, it not only equals, but surpasses that of the latter. Streamlike orientation and migration of lymphoid cells in the vicinity of blood vessels so characteristic in encephalitis is lacking in syphilis.

Among the exudates, the large mononuclear, hyperplastic and polyblastic differentiations of lymphocytes are decidedly less frequent in syphilis cerebri than in encephalitis. Macrophages only are found in the same proportion.

The described syphilitic lesions in the brain show a high ratio of plasma cells and a marked frequency of mast cells, both of the plasmamast cell type and of the histogenous variety. The greatest number of the plasma cells is encountered in paresis, in which, in the larger infiltrations, they constitute approximately one half of the exudate.

The plasma cells represent the terminal differentiation stage of lymphocytes and monocytes; they may, however, further differentiate into plasmamast cells, as originally outlined by Krompecher.

Associated with the degeneration of the plasma cells is the formation of Russell bodies (hyaline bodies) which at necrobiosis of the cell become

freely dispersed in the tissue. The Russell bodies are always conspicuously acidophilic. They vary in size from small eosinophil, granule-like structures to giant spheres of monocytic proportions.

In no way does the vascular or the newly formed capillary endothelium give rise to free wandering phagocytic cells. A detachment of the endothelial cells occurs frequently, but such cells either retain their characteristic endothelial aspect or become transformed into structures indistinguishable from fibroblasts, especially when somewhat receded from the vessel wall.

A heteroplastic formation of exudates from the so-called adventitial cells of Marchand or any other fixed connective tissue cells and amitosis in these cells are not noted.

Extravasation of red corpuscles into the adventitial spaces occurs rarely in syphilis, but in areas of softening, it may be massive.

Polymorphonuclear and eosinophil leukocytes play practically no rôle in this inflammatory process. The latter, however, are extremely numerous in areas of softening.

The formation of compound granular cells occurs occasionally about vessels; it is exceedingly marked in areas of softening in which emigrated lymphocytes may become transformed into gitter cells.

One case presents a widespread and marked hyalinization of parenchyma and blood vessels, especially of the capillary type. In two other cases, a mild (perhaps initial) process of hyalinization is noted about some of the capillaries.

Emigrating lymphocytes and monocytes are seen embedded in the hyaline matrix; because of this fact, they may well be termed "fossilized lymphoid cells."

IMMUNE CELLULAR REACTIONS IN EXPERIMENTAL ACUTE PERITONITIS *

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In a previous publication, it was demonstrated [1] that immunization with living colon bacilli prevents a fatal outcome in fecal peritonitis. No experimental evidence was offered to explain this immunity. It had been shown earlier that immunization with colon bacilli averts death in peritonitis due to *Bacillus coli* in gum tragacanth;[2] it is conceivable that the survival in this type of peritonitis is due to the production of specific antibodies. However, such an explanation cannot be readily offered when survivals occur following the intraperitoneal introduction of feces containing many other bacteria besides *B. coli.* Are the colon bacilli present in the feces solely responsible for the production of peritonitis and death? Is the immunity produced general and is it specific or nonspecific, or is one dealing with a peritoneal, cellular, nonspecific, local immunity? The experiments presented in this communication are attempts to answer, at least partly, these questions. We are presenting in this paper only the cellular reactions observed in the peripheral circulation, the peritoneal exudate and the tissues. The rôle of the so-called humoral elements will be presented in another communication.

EXPERIMENTAL PROCEDURES

Fecal material obtained from the lower part of the small bowel and the large bowel of dogs was mixed thoroughly with a 0.9 per cent sodium chloride solution and filtered through gauze. These prepared feces were injected into other dogs to produce acute fecal peritonitis. Four grams of feces in 20 cc. of saline solution was injected intraperitoneally into each animal.

A number of the dogs were immunized by intraperitoneal injections of living colon bacilli (our strain 300). The method of immunization was described in detail by Steinberg and Goldblatt.[3] Other dogs were immunized by subcutaneous

* Submitted for publication, Jan. 26, 1929.
* From the Division of Laboratories and Research, Toledo Hospital.
* This communication is a part of an experimental study on "Recovery in Peritonitis" made possible by a grant from the American Medical Association.

1. Steinberg, B., and Goldblatt, H.: Peritonitis: IV. Production of Active Immunity Against the Fatal Outcome of Experimental Fecal Peritonitis, Arch. Int. Med. **42**:415 (Sept.) 1928.

2. Goldblatt, H., and Steinberg, B.: Peritonitis: III. Active Immunization Against Experimental B. Coli Peritonitis, Arch. Int. Med. **41**:42 (Jan.) 1928.

3. Steinberg and Goldblatt (footnotes 1 and 2).

injections of living *B. coli*. A number of dogs were immunized by intraperitoneal injections of formaldehyde-killed *B. coli* (these, suspended in saline solution, were allowed to stand in 0.1 per cent formaldehyde for six hours). The same method of immunization was employed irrespective of the route or the state of the bacteria.

Prior to the production of the peritonitis, total and differential counts of the white cells of the peripheral blood were made. Following the onset of the peritonitis, total and differential counts of the white cells of the peripheral blood and of the peritoneal exudate were made at half hourly or hourly intervals. Supravital dyes (neutral red and janus green) were used in studying the peritoneal exudate, which was obtained by abdominal puncture with sterile glass capillary pipets. A neutral red stock solution was made up of 0.1 Gm. of the dye in 10 cc. of absolute alcohol; 0.5 cc. of the neutral red stock solution and 0.4 cc. of a saturated solution of janus green in absolute alcohol was added to 10 cc. of absolute alcohol. Dry smears were made from the dilute mixture of dyes. A drop of the peritoneal exudate was placed on the cover slip and inverted on the dry dye film. At short intervals, dogs were killed with chloroform and sections were taken from the omentum, parietal peritoneum, mesentery, diaphragm, intestine, mesenteric lymph node, liver, spleen and kidney, from approximately the same locations. The tissue was fixed in Zenker-formaldehyde without acetic acid and stained with hematoxylin-eosin and Gram stains. Thus, at short intervals following the onset of peritonitis, the peripheral blood, the peritoneal exudate and the tissue reactions were correlated.

Fecal Peritonitis in Normal, Nonimmune Animals.—In a previous communication, it was pointed out that when a sufficient amount of fecal material is injected into the peritoneal cavity of a dog, the animal develops a general peritonitis and succumbs within twenty-four hours. In these experiments, the duration of life of nonimmunized dogs with the peritoneum soiled with fecal material did not exceed eight hours. However, different samples and varying amounts of feces altered the survival period of the animals. In some of our experiments (unpublished), the intraperitoneal introduction of 2 Gm. of feces resulted in the survival of the animals for six days. We therefore used, for all the animals in these experiments, feces from the same stock, and administered it to them in equal amounts. Ten control dogs that had received injections of equal amounts of feces (4 Gm. in a 0.9 per cent sodium chloride solution) died in from seven to eight hours. It therefore became incumbent on us to study the cellular reactions within the first eight hours. Six dogs were used in the study of the cellular response to fecal peritonitis in normal nonimmune animals. One dog was allowed to die from the peritoneal infection; it died in seven and three-quarter hours after the onset of the infection. A second dog was killed at the end of one hour; a third at the end of two hours; a fourth at the end of three hours; a fifth at the end of four hours, and a sixth at the end of six hours after peritonitis was produced.

Fecal Peritonitis in Immune Animals.—The dogs were immunized by intraperitoneal injections of living colon bacilli (our strain 300, isolated from the blood of a patient dying with colon bacillus bacteremia). Thirteen dogs were used in this series. Twelve of these animals received intraperitoneally equal amounts of fecal material in saline solution (4 Gm. of feces in a 0.9 per cent sodium chloride solution); four of them were allowed to survive to confirm the efficacy of the immunization. The peritoneal exudate, the peripheral blood and the tissue reaction were studied in the other eight dogs. The animal that did not get any fecal material was killed and the tissues studied for reactions produced by the immunization. Of the eight dogs with fecal peritonitis, one was killed one hour after the

onset of peritonitis, another at the end of three hours, a third at the end of four hours, a fourth at the end of six hours, two at the end of eight hours, a seventh at the end of twelve hours, and the eighth at the end of twenty-four hours.

In the immunized dog without peritonitis, the total white cell count of the peripheral blood was 34,300. Polymorphonuclears constituted 91 per cent, mononuclears 4 per cent and lymphocytes 5 per cent. The peritoneal fluid showed only an occasional epithelial cell. The omentum and the parietal peritoneum contained cellular areas from 20 to 70 microns in width. The greater number of cells con-

TABLE 1.—*The Peripheral Blood and the Peritoneal Exudate in a Normal, Non-immune Dog with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis	Peripheral Blood		Peritoneal Exudate		
	Total White Count per C.Mm.	Differential Count	Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
(Prior to onset of peritonitis)	22,150	Polymorphonuclears.... 76% Lymphocytes 24%			
1	6,950	Polymorphonuclears.... 45% Lymphocytes 55%	1,300	Polymorphonuclears.... 81% Epithelial cells 14% Lymphocytes 5%	Polymorphonuclears.... 81% Mononuclears 19%
2	4,600	Polymorphonuclears.... 38% Lymphocytes 62%	6,200	Polymorphonuclears.... 86% Epithelial cells 9% Lymphocytes 5%	Polymorphonuclears.... 84% Mononuclears 16%
3	3,400	Polymorphonuclears.... 10% Lymphocytes 90%	27,750	Polymorphonuclears.... 90% Epithelial cells 8% Lymphocytes 2%	Polymorphonuclears.... 92% Mononuclears 8%
4	2,350	Polymorphonuclears.... 34% Lymphocytes 66%	26,950	Polymorphonuclears.... 91% Epithelial cells 7% Lymphocytes 2%	Polymorphonuclears.... 90% Mononuclears 10%
5	4,150	Polymorphonuclears.... 50% Lymphocytes 50%	26,300	Polymorphonuclears.... 95% Lymphocytes 5%	Polymorphonuclears.... 92% Mononuclears 8%
6	4,500	Polymorphonuclears.... 50% Lymphocytes 50%	14,900	Polymorphonuclears.... 89% Monocytes... 7% Lymphocytes 4%	Polymorphonuclears.... 88% Monocytes... 8% Mononuclears 4%
7	6,800	Polymorphonuclears.... 62% Lymphocytes 38%	14,100	Polymorphonuclears.... 80% Monocytes... 10% Lymphocytes 10%	Polymorphonuclears.... 80% Monocytes... 10% Mononuclears 10%
7¾	7,400	Polymorphonuclears.... 68% Lymphocytes 32%	14,400	Polymorphonuclears.... 86% Monocytes... 6% Lymphocytes 8%	Polymorphonuclears.... 84% Monocytes... 8% Mononuclears 8%

Outcome: Died 7¾ hours after onset of peritonitis.

sisted of large mononuclears, the remaining cells were plump and fusiform with fairly vesicular nuclei. These cells had the appearance of young fibroblasts; however, in the same sections, we observed similar cells sprouting from the endothelium of capillaries, and we are designating them here as endothelial cells. The capillaries were slightly dilated, and contained a small number of red cells and a few polymorphonuclears. In places, there was formation of new capillaries, the total picture being that of granulation tissue.

Immunization with Formaldehyde-Killed Bacteria and Production of Fecal Peritonitis.—An attempt to produce immunity against fecal peritonitis by the intraperitoneal injection of heat-killed *B. coli* did not prove successful.[1] Heat destroyed the greater part of the antigenic properties of the colon bacillus. As

a part of another experiment (in collaboration with Dr. H. Goldblatt), formaldehyde-killed *B. coli* (strain 300) were injected into six dogs intraperitoneally and into five dogs subcutaneously. The immunizing procedures were otherwise similar to those employed with living bacteria. Each of the eleven dogs received intra-

TABLE 2.—*The Peripheral Blood and the Peritoneal Exudate in an Immune Dog with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis	Peripheral Blood		Peritoneal Exudate		
	Total White Count per C.Mm.	Differential Count	Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
(Prior to onset of peritonitis)	40,200	Polymorphonuclears.... 95% Lymphocytes 5%			
1	27,000	Polymorphonuclears.... 92% Lymphocytes 8%	50,500	Polymorphonuclears.... 99% Epithelial cells 1%	Polymorphonuclears.... 99% Mononuclears 1%
2	12,500	Polymorphonuclears.... 90% Lymphocytes 10%	98,600	Polymorphonuclears.... 99% Epithelial cells 1%	Polymorphonuclears.... 99% Mononuclears 1%
3	4,300	Polymorphonuclears.... 83% Lymphocytes 17%	186,500	Polymorphonuclears.... 100%	Polymorphonuclears.... 98% Mononuclears 2%
4	8,750	Polymorphonuclears.... 79% Lymphocytes 21%	197,000	Polymorphonuclears.... 96% Mononuclears 2%	Polymorphonuclears.... 96% Monocytes... 4%
5	13,000	Polymorphonuclears.... 86% Lymphocytes 14%	216,000	Polymorphonuclears.... 93% Mononuclears 5%	Polymorphonuclears.... 93% Monocytes... 7%
6	23,700	Polymorphonuclears.... 84% Lymphocytes 16%	238,000	Polymorphonuclears.... 90% Mononuclears 10%	Polymorphonuclears.... 91% Monocytes... 7% Clasmatocytes 2%
7	26,400	Polymorphonuclears.... 82% Lymphocytes 18%	252,000	Polymorphonuclears.... 90% Lymphocytes 2% Mononuclears 8%	Polymorphonuclears.... 85% Monocytes... 8% Clasmatocytes 7%
8	43,500	Polymorphonuclears.... 81% Lymphocytes 19%	281,150	Polymorphonuclears.... 90% Mononuclears 10%	Polymorphonuclears.... 88% Monocytes... 10% Clasmatocytes 2%
9	48,500	Polymorphonuclears.... 82% Lymphocytes 18%	228,000	Polymorphonuclears.... 90% Mononuclears 10%	Polymorphonuclears.... 87% Monocytes... 8% Clasmatocytes 5%
10	50,000	Polymorphonuclears.... 87% Lymphocytes 13%	217,000	Polymorphonuclears.... 87% Mononuclears 13%	Polymorphonuclears.... 82% Monocytes... 10% Clasmatocytes 8%
11	52,000	Polymorphonuclears.... 92% Lymphocytes 8%	209,000	Polymorphonuclears.... 85% Mononuclears 15%	Polymorphonuclears.... 80% Monocytes... 8% Clasmatocytes 12%
12	57,000	Polymorphonuclears.... 92% Lymphocytes 8%	212,000	Polymorphonuclears.... 85% Mononuclears 15%	Polymorphonuclears.... 80% Monocytes... 11% Clasmatocytes 9%

Outcome: Killed at end of 12 hours after onset of peritonitis.

peritoneally 4 Gm. of feces in 20 cc. of a 0.9 per cent sodium chloride solution. All died in from seven to eighteen hours. Apparently, formaldehyde had destroyed all the antigenic properties of *B. coli*. The peripheral blood, the peritoneal exudate and the tissue of one of the dogs that received intraperitoneal injections of formaldehyde-killed bacteria were studied. The dog died in seven hours fifty minutes after the onset of peritonitis.

The peritoneal exudate, hour by hour, was similar to that observed in normal, nonimmune dogs with fecal peritonitis. Monocytes and clasmatocytes, however, appeared at the end of the fifth hour. At death, the clasmatocytes numbered 6 per cent and the monocytes 9 per cent. The omentum, the peritoneum and the mesentery showed mononuclears and endothelial cells, as observed in the sixth and eighth hour of fecal peritonitis in the immune dogs. The autopsy showed hemorrhagic peritonitis with little fibrin and 560 cc. of a cloudy, red, free fluid.

Subcutaneous Immunization with Living Colon Bacilli and Production of Fecal Peritonitis.—Three dogs were immunized subcutaneously with living colon bacilli. The immunizing method was the same as that employed in the intraperitoneal immunization. Each of the three animals received an intraperitoneal injection of 4 Gm. of

TABLE 3.—*The Peripheral Blood and the Peritoneal Exudate in a Dog (Immunized with Formaldehyde-Killed Bacteria) with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis	Peripheral Blood: Total White Count per C.Mm.	Peritoneal Exudate		
		Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
(Prior to onset of peritonitis)	19,850			
1	8,100	1,800	Polymorphonuclears 92% Lymphocytes..... 6% Epithelial cells..... 2%	Polymorphonuclears 98% Mononuclears..... 2%
2	5,200	3,040	Polymorphonuclears 96% Epithelial cells..... 4%	Polymorphonuclears 99% Mononuclears..... 1%
3	3,300	7,200	Polymorphonuclears 91% Lymphocytes..... 4% Epithelial cells..... 5%	Polymorphonuclears 93% Mononuclears..... 7%
4	2,700	11,000	Polymorphonuclears 94% Lymphocytes..... 2% Epithelial cells..... 4%	Polymorphonuclears 95% Mononuclears..... 5%
5	3,850	31,600	Polymorphonuclears 97% Mononuclears..... 3%	Polymorphonuclears 96% Monocytes..... 4% Clasmatocytes..... 1%
6	(Not taken)	(Not taken)	(Not taken)	(Not taken)
7	4,450	80,000	Polymorphonuclears 91% Mononuclears..... 9%	Polymorphonuclears 88% Monocytes..... 8% Clasmatocytes..... 4%
7¾	6,200	64,000	Polymorphonuclears 84% Mononuclears..... 10%	Polymorphonuclears 85% Monocytes..... 9% Clasmatocytes..... 6%

Outcome: Died 7¾ hours after onset of peritonitis.

feces in 20 cc. of a 0.9 per cent sodium chloride solution. Two of the animals were allowed to survive. The peritoneal exudate and the peripheral blood of the third were studied for twelve hours; then the dog was killed and the cellular reactions of the tissue were studied. The peritoneal exudate, during the twelve hours, showed a polymorphonuclear percentage that varied from 93 to 100. Monocytes appeared at the end of the third hour and never exceeded 6 per cent. The bacterial content of the peritoneal smears and the polymorphonuclear phagocytosis were similar to what had been seen in the case of the intraperitoneally immunized dogs. The omentum, the peritoneum and the mesentery at the end of twelve hours showed 91 per cent polymorphonuclears, 3 per cent mononuclears and 6 per cent endothelial cells. A number of polymorphonuclears in the tissue contained phagocytosed bacteria. The autopsy showed 721 cc. of a dirty gray fluid with some flakes of fibrin, a small amount of fibrin on some loops of bowel and a slight injection of the peritoneum, the mesentery and the diaphragm.

SUMMARY OF EXPERIMENTAL OBSERVATIONS

The white cells of the peripheral blood both in the immune and in the nonimmune animals appreciably decreased in number at the end of the first hour; this decrease continued and reached its lowest point at the end of four hours. From that hour the peripheral white cells began to increase in number. In nonimmune dogs, death occurred, as

TABLE 4.—*The Peripheral Blood and the Peritoneal Exudate in a Subcutaneously Immunized Dog with Fecal Peritonitis*

Time of Count in Hours after Onset of Peritonitis	Peripheral Blood		Peritoneal Exudate		
	Total White Count per C.Mm.	Differential Count	Total White Count per C.Mm.	Wright Stain Preparation	Vital Dye Preparation
(Prior to onset of peritonitis)	28,200	Polymorphonuclears.... 82% Lymphocytes 18%			
1	27,750	Polymorphonuclears.... 78% Lymphocytes 22%	9,500	Polymorphonuclears.... 100%	Polymorphonuclears.... 100%
2	18,600	Polymorphonuclears.... 81% Lymphocytes 19%	28,650	Polymorphonuclears.... 98% Lymphocytes 2%	Polymorphonuclears.... 100%
3	27,600	Polymorphonuclears.... 81% Lymphocytes 19%	67,600	Polymorphonuclears.... 99% Mononuclears 2%	Polymorphonuclears.... 99% Monocytes... 1%
4	32,100	Polymorphonuclears.... 80% Lymphocytes 20%	107,250	Polymorphonuclears.... 99% Mononuclears 1%	Polymorphonuclears.... 99% Monocytes... 1%
5	47,000	Polymorphonuclears.... 85% Lymphocytes 15%	180,000	Polymorphonuclears.... 96% Mononuclears 4%	Polymorphonuclears.... 98% Monocytes... 2%
6	45,000	Polymorphonuclears.... 89% Lymphocytes 11%	160,500	Polymorphonuclears.... 93% Mononuclears 7%	Polymorphonuclears.... 98% Monocytes... 2%
7	(Not taken)	(Not taken)	(Not taken)	(Not taken)	(Not taken)
8	42,500	Polymorphonuclears.... 91% Lymphocytes 9%	161,100	Polymorphonuclears.... 93% Mononuclears 7%	Polymorphonuclears.... 94% Monocytes... 6%
9	51,050	Polymorphonuclears.... 89% Lymphocytes 11%	160,500	Polymorphonuclears.... 95% Mononuclears 5%	Polymorphonuclears.... 98% Monocytes... 2%
10	70,500	Polymorphonuclears.... 86% Lymphocytes 14%	149,000	Polymorphonuclears.... 95% Mononuclears 5%	Polymorphonuclears.... 98% Monocytes... 2%
11	(Not taken)	(Not taken)	(Not taken)	(Not taken)	(Not taken)
12	79,200	Polymorphonuclears.... 88% Lymphocytes 12%	127,000	Polymorphonuclears.... 97% Mononuclears 3%	Polymorphonuclears.... 98% Monocytes... 2%

Outcome: Killed at end of 12 hours after onset of peritonitis.

a rule, before the white cells reached their normal level as determined before the infection. In immune dogs, the white cells increased in number from the fourth hour and in eight hours exceeded the pre-infection count. The immune animals evidenced a more ready mobilization of leukocytes following an initial leukopenia. The number of polymorphonuclears in the peripheral blood decreased relatively and absolutely with the decrease of the total number of the white cells, while the number of lymphocytes relatively increased. With the rise

of the total number of white cells, the previous polymorphonuclear-lymphocyte ratio was established.

Coincident with the fall of the peripheral leukocyte count, cells made their appearance in the peritoneal exudate. In fifteen minutes after the onset of the infection, cells were found in the exudate. In immune animals, cells appeared in greater number and more rapidly than in nonimmune dogs. At the end of the second hour, the cell count of an immune dog exceeded by from three to four times the largest number of cells of a nonimmune dog during any hour. The polymorphonuclears constituted, for the first three hours, from 98 to 100 per cent of the

Fig. 1.—Smear of the peritoneal exudate of fecal peritonitis one hour after onset in a normal, nonimmune dog. A large number of bacteria of various kinds may be seen, including three polymorphonuclear leukocytes. These do not show any phagocytosis.

cells in both the immune and nonimmune dogs. From the fourth hour, monocytes appeared in the immune animal. At the end of the sixth hour, clasmatocytes began to appear. At the end of eight hours, both monocytes and clasmatocytes constituted approximately 12 per cent of the total number of cells, the other cells being polymorphonuclears. In nonimmune animals, monocytes appeared at the end of the sixth hour and constituted from 8 to 10 per cent of the total number of cells.

The polymorphonuclears showed marked phagocytic activities in non-immune animals. Practically all the polymorphonuclears were loaded with

bacteria, but there were apparently too many bacteria for the number of cells; there were large numbers of free bacteria throughout the course of the infection. In immune animals, practically all the bacteria were phagocytosed at the end of two hours and, owing to the large number of cells, only some of them contained bacteria. As far as the peritoneal exudate was concerned, the struggle with the bacteria was over in two or three hours. The tissue of the nonimmune dogs showed a paucity of leukocytes. At the end of seven and three-quarter hours, the tissue of the nonimmune animal with the largest number of polymorphonuclears at its disposal actually had far less polymorphonuclears than an immune animal at the end of an hour after the onset of peritonitis. The polymorphonuclears of the tissue were likewise phagocytic. In the

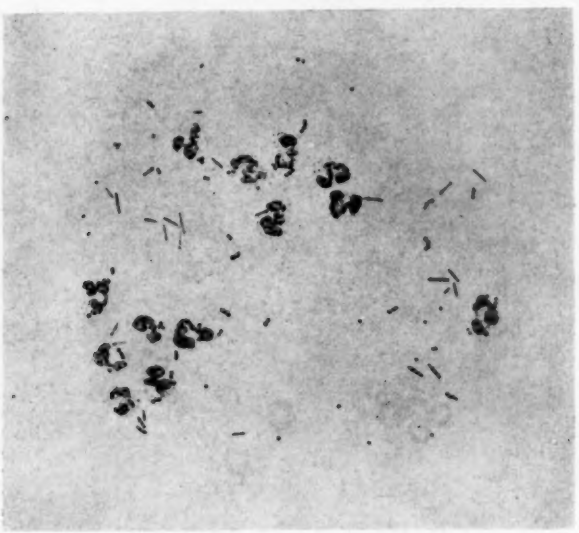

Fig. 2.—Smear of the peritoneal exudate of fecal peritonitis seven and three-quarter hours after onset in a normal, nonimmune dog. A large number of bacteria of various kinds may be seen, including twelve polymorphonuclears, most of them containing phagocytosed bacteria.

fourth hour, the tissue of the immune animal showed a number of mononuclear cells with ingested red and white cells.

Intraperitoneal injections of formaldehyde-killed bacteria, which do not immunize, evoked in a fecal peritonitis a peritoneal exudate which at the end of seven and five-sixth hours showed a small number of white cells, with the monocytes and clasmatocytes constituting 15 per cent.

Subcutaneous immunization, which resulted in an actual immunity, produced a rapid mobilization of cells in the peripheral blood and a large number of cells in the peritoneal exudate, which contained only 2 per cent monocytes, and 98 per cent polymorphonuclears.

COMMENT

The purpose of this work was essentially to determine the character of the cellular activity in fecal peritonitis following active immunization with colon bacilli. However, the results of the experiments placed us in the midst of a controversy as to the type of cell responsible for the immunity and as to whether the immunity produced is local. This controversy began, in part, with Metchnikoff,[4] who asserted that the polymorphonuclears (microphages) are the phagocytic cells and that the mononuclears (macrophages) are not concerned with phagocytosis of bacteria but rather with the disposal of disabled microphages. Since

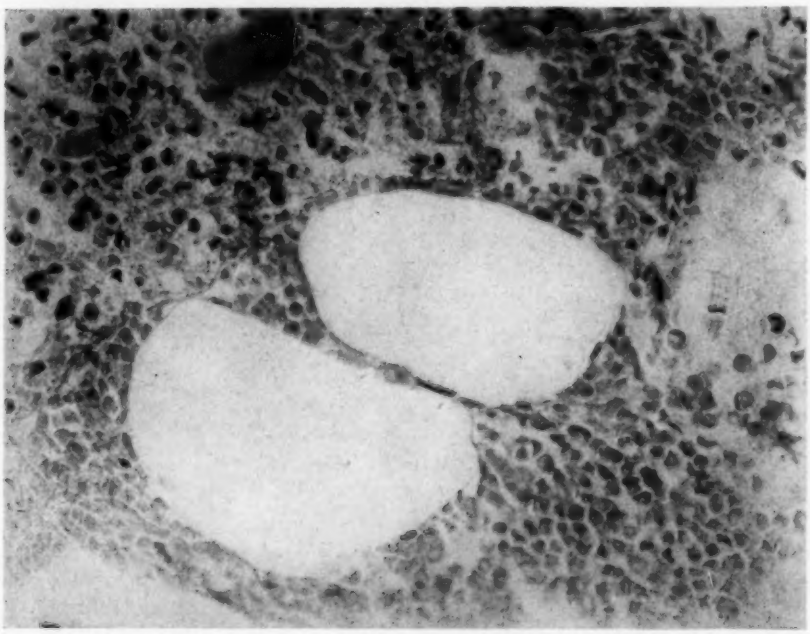

Fig. 3.—Section of omentum at the end of seven and three-quarter hours of fecal peritonitis in a normal, nonimmune dog. A moderate number of polymorphonuclears and mononuclears may be seen.

then, other investigators have observed that the mononuclears phagocytose not only polymorphonuclears but also bacteria; these mononuclears have been variously termed clasmatocytes by Ranvier, adventitial cells by Marchand, pyrrhol cells by Goldman, endothelial leukocytes by Mallory, polyblasts by Maximow and round rhagiocrins by Renaut. Durham,[5] Bordet,[6] Wallgren,[7] Buxton and Torrey,[8] Zange-

4. Metchnikoff, E.: Virchows Arch. f. path. Anat. **107**:209, 1887.
5. Durham, A. E.: J. Path. & Bact. **4**:338, 1897.
6. Bordet, J.: Ann. de l'inst. Pasteur **11**:177, 1897.
7. Wallgren, A.: Beitr. z. path. Anat. u. z. allg. Path. **25**:206, 1899.
8. Buxton, B. H., and Torrey, J. C.: J. M. Research **15**:3, 1906.

meister and Gans [9] and Kanai [10] were some of the investigators who observed phagocytosis of bacteria by mononuclears and ascribed to these mononuclears the chief rôle in the disposal of the bacteria. Besredka [11] introduced the conception of local immunity and Gay [12] and his collaborators associated these mononuclears, or clasmatocytes, with local immunity. Gay and his co-workers asserted that the formation of antibodies is coincident with the appearance of clasmatocytes and that local protection is dependent on a local increase in the number of clasmatocytes.

Other investigators, among them von Büngner,[13] Helly,[14] Cunningham [15] and Freedlander and Toomey,[16] observed that there was a preponderance of polymorphonuclears within the first twenty-four hours after the introduction of bacteria or particulate matter. Metalnikov

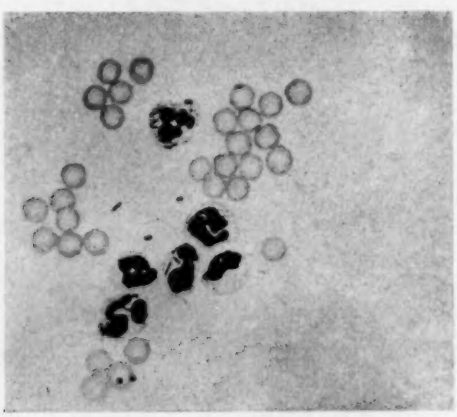

Fig. 4.—Smear of the peritoneal exudate of fecal peritonitis one hour after onset in an intraperitoneally immunized dog. There are six polymorphonuclears containing many phagocytosed bacteria. There are only three free bacteria.

9. Zangemeister, W., and Gans, H.: München. med. Wchnschr. **56**:793, 1909.

10. Kanai, S.: Verhandl. d. jap. path. Gesellsch. **1**:126, 1919.

11. Besredka, A.: Ann. de l'inst. Pasteur **35**:421, 1921; Local Immunization: Specific Dressings, trans. by Plotz, Baltimore, Williams & Wilkins, 1927.

12. Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**:338, 1923. Gay, F. P.: Physiol. Rev. **4**:191, 1924. Gay, F. P., and Linton, R. W.: Proc. Soc. Exper. Biol. & Med. **23**:325, 1926. Gay, F. P.; Clark, A. R., and Linton, R. W.: A Histologic Basis for Local Resistance and Immunity to Streptococcus: VII. Studies in Streptococcus Infection and Immunity, Arch. Path. **1**:857 (June) 1926.

13. Von Büngner: Beitr. z. path. Anat. u. z. allg. Path. **19**:33, 1896.

14. Helly, K.: Beitr. z. path. Anat. u. z. allg. Path. **37**:171, 1905.

15. Cunningham, R. S.: Am. J. Physiol. **59**:1, 1922.

16. Freedlander, S. O., and Toomey, J. A.: J. Exper. Med. **47**:663, 1928.

and Toumanoff,[17] in a recent article, again demonstrated the early appearance of polymorphonuclears in the peritoneal cavity and observed a more rapid phagocytosis in vaccinated animals and the late appearance of clasmatocytes.

In our experiments, the criterion of a successful immunization was survival of the animal. Lack of immunity resulted in death. Our work suggests that the issue of death or survival under the conditions of the experiments is decided within the first eight hours after the onset of the infection. This assumption is based on the death of the

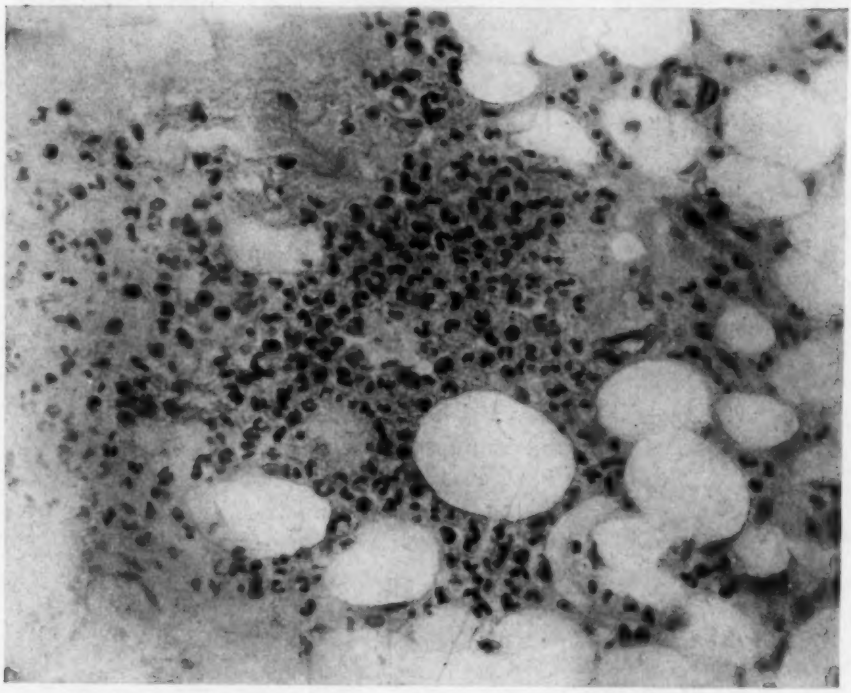

Fig. 5.—Section of omentum at the end of one hour of fecal peritonitis in an intraperitoneally immunized dog. There is a fairly large number of polymorphonuclears free in the tissue.

control nonimmune animals within eight hours, and the practically total disposal of the free bacteria in the immune animals within those hours. If this assumption is true, the polymorphonuclear is apparently the cell essentially concerned with the primary disposal of the bacteria in the immunized animals with fecal peritonitis.

It is not within the scope of this paper to follow the fate of the polymorphonuclears after the phagocytosis of bacteria. The observa-

17. Metalnikov, S., and Toumanoff, K.: Ann. de l'inst. Pasteur **38**:22, 1925.

tions of investigators from Metchnikoff to Freedlander and Toomey agree as to the capacity of the clasmatocyte to phagocytose polymorphonuclears. Metchnikoff's contention that the function of clasmatocytes is to remove damaged microphages is further amplified by the assumption of Freedlander and Toomey that the ingestion of polymorphonuclears with bacteria by clasmatocytes prevents a recurrence of bacterial activity. That such a recurrence of bacterial activity on the death of the cell is possible is suggested by the original demonstration by Metchnikoff (quoted by Besredka [18]) of viable phagocytosed bacteria within polymorphonuclears from ten to twelve days after phagocytosis.

Since most of the immunization was done intraperitoneally, it should have been possible to establish a local immunity. Local immunity as defined by Gay [19] "is an acquired, increased protection of some part of tissue superior to that existent elsewhere in the body. It is further a locally superior mechanism for the disposal of the particular microorganism rather than a local mobilization of antibodies generally present in the body." Under the conditions of our experiments, we failed to observe any particular increased local cellular protection. The cellular response in the peritoneal cavity following colon bacillus immunization and fecal peritonitis was apparently a local mobilization of a general increase in cellular activity. The local peritoneal picture of granulation tissue in the immunized dog (Gay and his co-workers called attention to the thickening of the pleura in immunized animals) without peritonitis we assumed to be a healing inflammatory reaction in response to the introduction of an irritant—in this instance, colon bacillus. Furthermore, our subcutaneously immunized animal was as readily protected and showed a local reaction as rapid and extensive as did the intraperitoneally immunized dogs. Attempted intraperitoneal immunization with formaldehyde-killed colon bacilli resulted in peritoneal granulation tissue (observed in the dog with twelve hour peritonitis) but not in immunity. It is not unlikely that this granulation tissue is more prepared to combat infection than normal tissue; it is more vascular and hence commandeers more cells; and it contains the later cells of the healing process. However, in our experiments, this granulation tissue alone was not sufficient to establish immunity. Other factors, which were responsible for the ready mobilization of polymorphonuclears, were necessary.

SUMMARY

Active immunization with living colon bacilli, followed by fecal peritonitis, resulted in the first twenty-four hours in a cellular reaction

18. Besredka (footnote 11, second reference).
19. Gay (footnote 12, first reference).

which was predominantly polymorphonuclear. The bacteria in the peritoneal cavity were phagocytosed largely by polymorphonuclears, and the phagocytosis was practically complete at the end of the first eight hours after the onset of peritonitis. The polymorphonuclears, evoked by colon bacillus immunization, acted as phagocytes of other bacteria in the peritoneal exudate than *B. coli*. The difference in the cellular reaction in the peritoneal exudate, the peripheral blood and the tissue between a nonimmune and an immune animal, under the conditions of these experiments, was quantitative. The immune animal mobilized polymorphonuclears more rapidly and mobilized a far greater number of them than the nonimmune animal. The factor in the colon bacillus that evoked this cellular activity was destroyed entirely by formaldehyde. The presence of white cells in the peritoneal exudate of immune animals with peritonitis apparently represented a local manifestation of a general mobilization of these cells. The polymorphonuclears in the general circulation were apparently the first cells to appear at the point of bacterial invasion, and therefore they probably represented the first line of cellular defense against the bacterial infection.

THE PATHOLOGIC ANATOMY IN TWENTY-EIGHT CASES OF ADDISON'S DISEASE *

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In the original description of the disease which bears his name, Thomas Addison defined it as "a remarkable progressive feebleness of the patient without any apparent known cause, or as it is styled, asthenia, a discoloration of the skin and a disease of the suprarenal capsules."[1] Wilks,[2] who studied the pathologic anatomy in Addison's first cases, in 1862 and 1865 reported a total of thirty-three cases which coincided with the entity which Addison described. He included five of Addison's original cases, but discredited the others as not conforming to the entity and not intended to be included by Addison himself. Wilks described the suprarenal glands in the series as scrofulous and totally destroyed. Because the necrosis in the suprarenal glands did not resemble the necrosis ascribed to tuberculosis at that time, he was rather of the opinion that the glands presented a unique disease not identical with other tuberculous processes. In many of his cases were small tuberculous lesions of other parts of the body, both healed and active, but in none were these extensive. Wilks' excellent description of the gross aspect of the suprarenal glands, however, leaves little doubt that the lesions were the same as lesions that have been seen many times since and identified as tuberculosis by histologic study. Wilks mentioned enlarged lymph nodes and hyperplasia of the intestinal lymphoid tissue in several cases. He noted that the hearts were rather small, and in a few of the cases described another curious and still unexplained phenomenon, hyperplasia of Brunner's glands. In 1885, Coupland[3] reported a case of clinical Addison's disease in which both suprarenal glands were found to be markedly atrophic. He was able to find five

* Submitted for publication, April 22, 1929.

* From the Division of Medicine, the Mayo Clinic.

* Work done in the Section on Pathologic Anatomy.

1. Wilks, Samuel, and Daldy: On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules, in: A Collection of the Published Writings of Thomas Addison, London, The New Sydenham Society, 1868, p. 211.

2. Wilks, Samuel: On Disease of the Supra-Renal Capsules; or, Morbus Addisonii, Guy's Hosp. Rep. **8**:1, 1862; Additional Cases of Supra-Renal Disease with Remarks, ibid. **11**:23, 1865.

3. Coupland, Sidney: Atrophy of Adrenals with Addison's Disease, Tr. Path. Soc. Lond. **36**:423, 1885.

similar cases in the literature. In 1892, Lewin [4] made an extremely comprehensive review of the literature up to that time.

Unfortunately, Addison's original description was used somewhat loosely and numerous cases were reported merely because the patients had brownish pigmentation of the skin with or without suprarenal lesions. Also many suprarenal lesions of different types, unilateral and bilateral, small and extensive, were reported as being caused by Addison's disease without the typical clinical syndrome. Lewin's two series included 871 cases. These are difficult to tabulate because they were described by so many different authors in so many different ways. Lewin cited 639 of these as typical cases; the suprarenal glands were normal in 72 of them and in 233 there was no pigmentation. Among the diseased conditions of the suprarenal glands, tuberculosis or probable tuberculosis was found in 254. Bacilli of tuberculosis were said to have been found in the suprarenal glands in seven cases. A few cases were described as being cases of atrophy or degeneration, carcinoma, cysts, amyloidosis, gumma, echinococcus cysts and complete aplasia. The pathologic anatomy of the suprarenal glands in the other cases was not definitely reported. There was associated pulmonary tuberculosis in 256 cases, and renal tuberculosis in 16. In 1907, Hedinger [5] reported a series of fifteen cases of Addison's disease, in fourteen of which there was tuberculosis and in one case atrophy of the suprarenal glands. He stressed the fact that a status thymicolymphaticus was found in seven cases, including the case of atrophy, and that in five more there was generalized hyperplasia of the lymph nodes.

The largest recent series was reported by Coneybeare and Millis,[6] and comprised twenty-nine cases with necropsies, observed in Guy's Hospital between 1904 and 1923. Of these, there was bilateral fibrocaseous tuberculosis of the suprarenal glands in twenty-two and simple atrophy in six. In one case, suprarenal tissue was not found. In the twenty-two cases of tuberculosis of the suprarenal glands, there was active tuberculosis elsewhere in the body in six, and in all there were tuberculous scars in the lungs. The question of gumma of the suprarenal glands as a cause of Addison's disease was discussed by Schaffner and Howard [7] in 1916. They cited two cases described by Taylor and one by Jacquet and Segary in which *Treponema pallidum* was demonstrated. Amyloidosis of the suprarenal glands has been described

4. Lewin, G.: Ueber Morbus addisonii, Charité-Ann. **17**:536, 1892.

5. Hedinger, Ernst: Ueber die Kombination von Morbus addisonii mit Status lymphaticus, Frankfurt. Ztschr. f. Path. **1**:527, 1907.

6. Coneybeare, J. J., and Millis, G. C.: Observations on Twenty-Nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904 and 1923, Guy's Hosp. Rep. **74**:369, 1924.

7. Schaffner, P. M., and Howard, Tasker: Addison's Disease of Syphilitic Origin: Report of a Case, New York M. J. **103**:1026, 1916.

several times since Lewin's article appeared. Most of the clinical descriptions of these cases are not convincing, but the cases of Bittorf,[8] Schlesinger,[9] McCutcheon,[10] Hunter and Rush[11] and Philpott[12] seem fairly typical. In 1926, Loeper and Ollivier[13] described a case of bilateral fatty transformation of the suprarenal glands with typical addisonian symptoms. As has been mentioned, various cases of carcinoma have been reported. Greenhow[14] reported two cases and Bristow one case of complete destruction of the suprarenal glands by carcinoma. Pigmentation was not present in any of these cases. Wilks was rather emphatic in stating that carcinoma of the suprarenal glands was not a cause of Addison's disease. The cases of atrophy are interesting. Recently, Brenner[15] reported five cases and commented on the subject in considerable detail. He rejected the theory that the condition is congenital hypoplasia of the glands associated with a status thymicolymphaticus and does not believe that it is identical with healed atypical tuberculosis or with any other condition that can be identified. Chronic inflammation of indefinite etiology is questionable as a cause of atrophy. Brenner inclined more toward the opinion that the condition is one of simple atrophy, possibly due to slow necrosis from some toxin with special affiinty for the suprarenal glands. The remaining cells undergo compensatory hypertrophy and multiply to form adenoma-like nodules. These cells are again attacked or undergo atrophy of exhaustion. The cortex is primarily involved and later the medulla. In Kiefer's[16] case, adenoma-like regeneration was striking. Recently, Philpott reported 14 cases of Addison's disease found in the course of 2,550 consecutive necropsies. The suprarenal lesions were as follows: tuberculosis, seven; metastatic carcinoma, four; mycosis fungoides, one; simple atrophy, one, and amyloidosis, one.

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8. Bittorf, A.: Beiträge zur Pathologie der Nebennieren, Deutsches Arch. f. klin. Med. **100**:116, 1910.

9. Schlesinger, Hermann: Subakute Insuffizienz der Nebennieren bei Amyloidose, nebst Bemerkungen über den Morbus addisonii, Wien. klin. Wchnschr. **30**:99, 1917.

10. McCutcheon, Morton: The Relation of Addison's Disease to Amyloidosis, Am. J. M. Sc. **166**:197, 1923.

11. Hunter, W. C., and Rush, H. P.: Amyloidosis of the Adrenals as a Cause of Addison's Disease, Ann. Clin. Med. **5**:404, 1926.

12. Philpott, N. W.: Addison's Disease in Association with Amyloidosis, Ann. Int. Med. **1**:613, 1927-1928.

13. Loeper, M., and Ollivier, J.: Métamorphose adipeuse des deux capsules surrenales avec metanodermie, Bull. et mém. Soc. méd. d. hôp. de Paris **2**:312, 1926.

14. Greenhow, E. H.: Cancer of the Supra-Renal Capsules, Tr. Path. Soc. Lond. **24**:238, 1872-1873.

15. Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Supra-Renals, Quart. J. M. **22**:121, 1928.

16. Kiefer, Hans: Addisonsche Erkrankung infolge chronischer Nebennierendystrophie mit adenomartigen Regeneraten, Arch. f. path. Anat. **265**:472, 1927.

TABLE 1.—*Summary of Pathologic Anatomy of Suprarenal Glands*

Case	Necropsy, Year	Age and Sex	Suprarenal Glands		Acid-Fast Bacilli in Tissue	Suprarenal Tissue Remaining
			Gross	Histologic		
1	1910	35 M	Both enlarged, typical fibrosis with necrotic areas	Advanced tuberculosis, proliferative type	—	A few small islands of cortex; a few hypertrophic adenomas
2	1914	47 M	Left large with typical necrosis; right small fibrous mass	Advanced tuberculosis, proliferative and necrotic type	—	Several small islands of cortex
3	1915	43 M	Both enlarged, typical necrosis	Advanced tuberculosis, necrotic type, very inactive	—	A few small islands of cortex; a few hypertrophic adenomas
4	1917	39 M	Both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few hypertrophic adenomas
5	1917	40 F	Right enlarged, typical necrosis; left encapsulated abscess	Advanced tuberculosis, necrotic type	—	Several small islands of cortex; several hypertrophic adenomas
6	1920	40 F	Both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	..	None*
7	1921	41 M	Right large, typical necrosis; left small, typical necrosis	Advanced tuberculosis, proliferative type	..	Several small islands of cortex; many hypertrophic adenomas
8	1922	32 M	Both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few hypertrophic adenomas
9	1923	31 M	Both very small and dark brown	Marked atrophy with some nonspecific chronic inflammatory reaction	..	Approximately 5 per cent of cortex and 20 per cent of medulla
10	1923	55 M	Both enlarged, 24 and 15 Gm.; typical necrosis	Advanced tuberculosis, necrotic type	..	A few small islands of cortex; a few hypertrophic adenomas
11	1924	25 M	Both enlarged, 16 and 16 Gm.; typical necrosis	Advanced tuberculosis, necrotic type	..	A few small islands of cortex; a few hypertrophic adenomas
12	1925	69 M	Both slightly enlarged, typical necrosis	Moderately advanced tuberculosis, necrotic type	+ (many)	Approximately 10 per cent of cortex
13	1925	33 M	Left complete calcification; right two very small nodules	Right, advanced atrophy	..	Approximately 5 per cent of right suprerenal gland
14	1925	50 M	Both typical necrosis	Advanced tuberculosis, proliferative type	+ (few)	Several small areas of cortex; many hypertrophic adenomas
15	1925	34 M	Very large, 27 and 28 Gm.; both typical necrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few small islands of cortex; a few hypertrophic adenomas
16	1925	35 F	Normal size, both typical necrosis	Advanced tuberculosis, necrotic type	+ (few)	Several hypertrophic adenomas
17	1925	40 F	Both normal size; necrosis with marked calcification	Advanced tuberculosis, necrotic type with marked calcification	..	A few small islands of cortex
18	1925	65 M	Both small, typical necrosis	Advanced tuberculosis, necrotic type	—	A few small islands of cortex; a few hypertrophic adenomas
19	1925	26 M	Both typical necrosis with abscesses	Advanced tuberculosis, proliferative type with abscesses	+ (few)	Many hypertrophic adenomas
20	1927	45 F	Both typical necrosis	Advanced tuberculosis, necrotic type	+ (many)	A few small islands of cortex; a few hypertrophic adenomas

* Material for complete study not available.

TABLE 1.—*Summary of Pathologic Anatomy of Suprarenal Glands—Continued*

Case	Necropsy, Year	Age and Sex	Suprarenal Glands		Acid-Fast Bacilli in Tissue	Suprarenal Tissue Remaining
			Gross	Histologic		
21	1927	48 M	Both typical necrosis, enlarged, 23 and 21 Gm.	Advanced tuberculosis, proliferative and necrotic type	+ (few)	Several small islands of cortex
22	1927	45 M	Both typical necrosis	Advanced tuberculosis, necrotic type	+ (few)	A few small islands of cortex; many hypertrophic adenomas; one small island of medulla
23	1927	58 M	Right small, left large, both typical necrosis	Advanced tuberculosis, necrotic type	+ (many)	A few small islands of cortex; a few hypertrophic adenomas
24	1927	48 M	Normal size; both typical necrosis	Advanced tuberculosis, proliferative type	+ (few)	Many hypertrophic adenomas
25	1927	37 M	Marked atrophy, 0.9 and 1.2 Gm.; dark brown	Advanced atrophy	..	Approximately 10 per cent cortex and medulla
26	1927	32 M	Enlarged, 12 and 18 Gm.; both typical necrosis	Advanced tuberculosis, proliferative type	+ (few)	A few hypertrophic adenomas
27	1928	46 M	Both enlarged, typical necrosis	Advanced tuberculosis, necrotic type	+ (few)	A few small islands of cortex; a few hypertrophic adenomas
28	1929	28 F	Left large, 26 Gm.; typical necrosis; right small, 10 Gm.; necrosis and fibrosis	Advanced tuberculosis, proliferative and necrotic type	—	A few small islands of cortex; several hypertrophic adenomas

MATERIAL FOR STUDY

In the past eighteen years, at the Mayo Clinic, necropsies have been performed in twenty-eight cases in which the clinical syndrome of Addison's disease had been present. In 1925, Rowntree [17] briefly commented on eight of these cases with regard to the observations at necropsy. A review of the protocols and reexamination of all the material available from these twenty-eight necropsies form the basis for this study.

A summary of the condition of the suprarenal glands in these twenty-eight cases is given in table 1. The typical brownish pigmentation of the skin was seen in all of these cases at the time of necropsy except in cases 13 and 22. In case 13 pigmentation had been present previously but at the last admission of the patient it apparently had cleared up entirely. In case 22 pigmentation never had been present. The case was reported by Ghrist and Rowntree [18] in 1927.

LESIONS OF THE SUPRARENAL GLANDS

Tuberculosis.—In twenty-five of the twenty-eight cases, there was a lesion of the suprarenal glands which on histologic examination was called tuberculosis. In the sections of all of these, there were typical

17. Rowntree, L. G.: Studies in Addison's Disease, J. A. M. A. **84**:327 (Jan. 31) 1925.

18. Ghrist, D. G., and Rowntree, L. G.: Addison's Disease Without Pigmentation: Report of a Case, Endocrinology **2**:589, 1927.

areas consisting of tubercles with endothelioid cells, giant cells, fibroblasts and lymphocytes. Since the absolute diagnosis of tuberculosis rests on the observation of the bacilli in the lesions, or in material obtained from the lesions, sections 5 microns thick cut from nineteen of the tuberculous suprarenal glands were stained with the Ziehl-Neelsen stain. Acid-fast bacilli morphologically resembling bacilli of tuberculosis were found in these sections in eleven cases. It will be noted that in the material from necropsies in 1925, or later, bacilli of tuberculosis were found in eleven of fourteen cases, and that they were not found in the material from any of the necropsies before 1925.

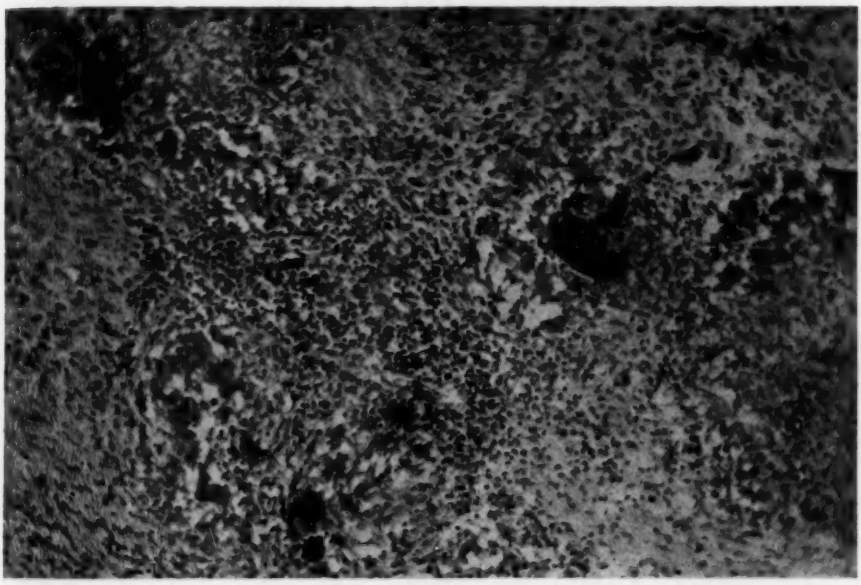

Fig. 1.—Tuberculosis of the suprarenal gland, of the active proliferative type; × 150.

A posible explanation for this may be the fact that the tissue from which the sections were cut had been in a diluted solution of formaldehyde, U. S. P. (1 : 10) for more than four years, and it is thought that with fresh tissue the percentage would be considerably higher. The bacilli were found in areas of necrosis, especially near their margins, and not in the tubercles, giant cells or endothelioid cells.

In considering the histologic appearance of sections from these glands, the tuberculosis was found to be bilateral in all the twenty-five cases and involved the entire gland, with almost complete destruction. The type of lesion varied between two extremes, a very proliferative type with many tubercles, many fibroblasts and connective tissue cells

and only small areas of necrosis (fig. 1), and a type in which the gland was a mass of necrosis surrounded by a fibrous capsule in which there were only a few tubercles and a small number of lymphocytes (fig. 2).

The necrosis consisted of a homogeneous mass that took the eosin stain, and in which there were occasionally fine particles of calcium and often fat droplets near the margins. Grossly, the necrosis differed from the ordinary caseous necrosis of tuberculosis in that the necrotic process was yellow or yellowish gray, firm and rubbery and on section presented a uniform surface. This gross picture is well known to pathologists as being characteristic of Addison's disease and differing from most tuberculous necrosis found in other parts of the body. Gross sections of the glands in the more active proliferative types were more or less mottled and apparently nodular, and were more of a pink or pinkish brown than sections from the glands in the less active cases. As a rule, the glands were found to be definitely enlarged. The largest pair weighed 27 and 28 Gm., respectively, compared with a normal weight of from 4 to 10 Gm. In some cases one tuberculous gland was large and the other was normal in size. The glands were not smaller than normal in any case. In only one case (case 17) was there any gross calcification. In this case both suprarenal glands were slightly larger than normal, and about half the substance was replaced by calcium salts.

A definite line of distinction cannot be made among the different types of tuberculous lesions in the suprarenal glands. Of the twenty-five cases in which there were tuberculous lesions in this series, the lesions were essentially proliferative, with many tubercles and little necrosis, in seven cases; proliferative and necrotic, with a moderate number of tubercles and moderate necrosis, in eight cases; essentially necrotic, with extensive encapsulated necrosis with few tubercles, in eight cases, and inactive, accompanied by encapsulated necrosis, with or without calcium deposits, and a few foci of lymphocytes, in two cases.

Certain other observers have stated that the suprarenal glands were completely destroyed by the tuberculous process. Whenever possible, numerous sections of the glands were examined to determine whether any suprarenal tissue remained. It is notable that some cortical tissue was found in twenty-four of the twenty-five cases. In the one case in which it was not found only one section from each gland was available for study, so the data may be considered incomplete. The remaining suprarenal tissue was seen only as small islands of cortex near the periphery (fig. 3) or as cortical adenomas near or beyond the margin of the tuberculous process (fig. 4). The remaining suprarenal cells were usually hypertrophic and moderately hyperchromatic. The nuclei were large and deeply staining and usually there was a brown pigment, probably melanin, uniformly distributed through the cytoplasm. The amount

of this suprarenal cortical tissue was always very small when compared with the total amount in a normal adult and was estimated at less than 5 per cent of the normal amount.

In only one case was any of the medulla of the suprarenal glands seen, and in this case the amount was in a small area. This case, however, was the only one of the series in which there was no pigmentation.

In order to have some conception of the method of development of suprarenal tuberculosis, eight cases were studied in which there were early tuberculous lesions. In none of these cases were there clinical symptoms of Addison's disease. In four cases, the process involved only one suprarenal gland and in four, both glands. In three of these

Fig. 2.—Advanced tuberculosis of the suprarenal gland, of the encapsulated necrotic type; × 150.

eight cases there was associated generalized miliary tuberculosis; in two, renal tuberculosis; in one case tuberculous spondylitis, and in two cases there were healed tuberculous lesions in other parts of the body but other active foci were not found. The maximal amount of suprarenal destruction was approximately 80 per cent of both glands in the case of tuberculous spondylitis. In the others, more than 50 per cent of normal suprarenal tissue remained.

The lesions in these early cases were situated rather consistently in two places: either at some distance from the main suprarenal vein in the medulla or in deep layers of the cortex or else midway in the cortex between the medulla and the outer surface. The larger lesions

seemed to have spread centrifugally until they extended through practically the full thickness of the gland. The lesions consisted mainly of regions of necrosis which stained deeply with eosin and were surrounded by a rather narrow margin of lymphocytes in which there were a few tubercles and giant cells. There were comparatively few connective tissue fibers or fibroblasts. The lymphocytes extended into the surrounding tissue only for a short distance. Apparently the lesion was spreading without much resistance on the part of the gland.

From the appearance of early and late tuberculous lesions of the suprarenal glands, certain generalizations are suggested. One type of the lesion apparently encounters active resistance and much cellular

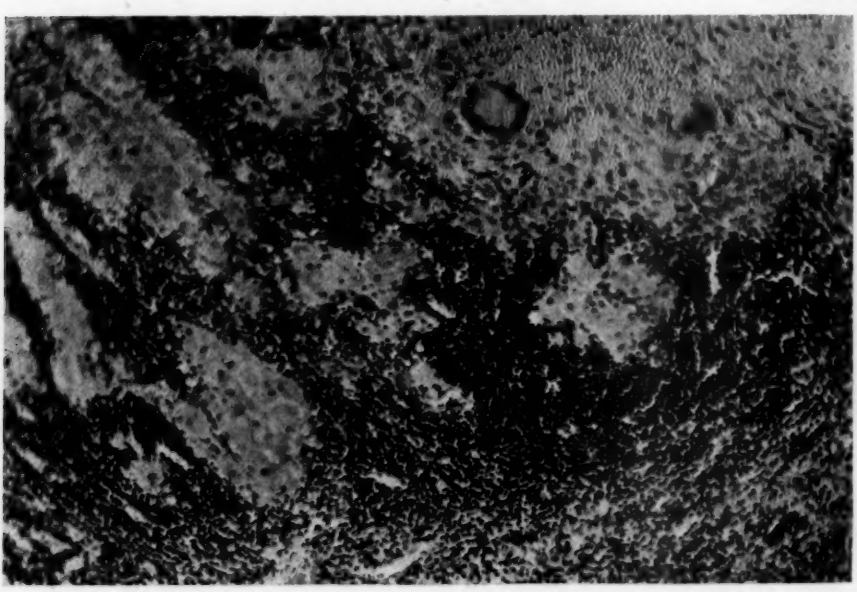

Fig. 3.—Advanced tuberculosis of the suprarenal gland with an island of cortical cells in the inflammatory tissue; × 150.

proliferation, which, together with some necrosis, gradually destroys the gland. Another type encounters little resistance; areas of necrosis gradually spread until the gland is practically destroyed, and the necrotic mass becomes encapsulated. Between these two types there are intermediate types.

The process apparently starts in the medulla or midcortical region, and spreads centrifugally. The medulla and the suprarenal veins must be destroyed rather early in the process and the last portions of the gland to be involved are the outer layers of the cortex and any cortical adenomas which may lie beyond. Hence the arterial supply, coming from several vessels which tend to ramify on the surface, is involved

rather late in the process. As the gland nears complete destruction, the remaining cortical cells tend to hypertrophy and become deeply pigmented. It is difficult to determine whether there is an increase in the number of cells in the adenomas or whether there is merely hypertrophy of the cells already present. The type of necrosis is usually peculiar to the organ and may be due to the blood supply or to the lipoid and melanin content of the gland. From observations on suprarenal glands from approximately 1,000 necropsies at The Mayo Clinic small areas of healed tuberculous lesions, such as those which are found in the lungs, liver and spleen, have not been found in the suprarenal glands. Robertson,[19] with a much larger experience in necropsy

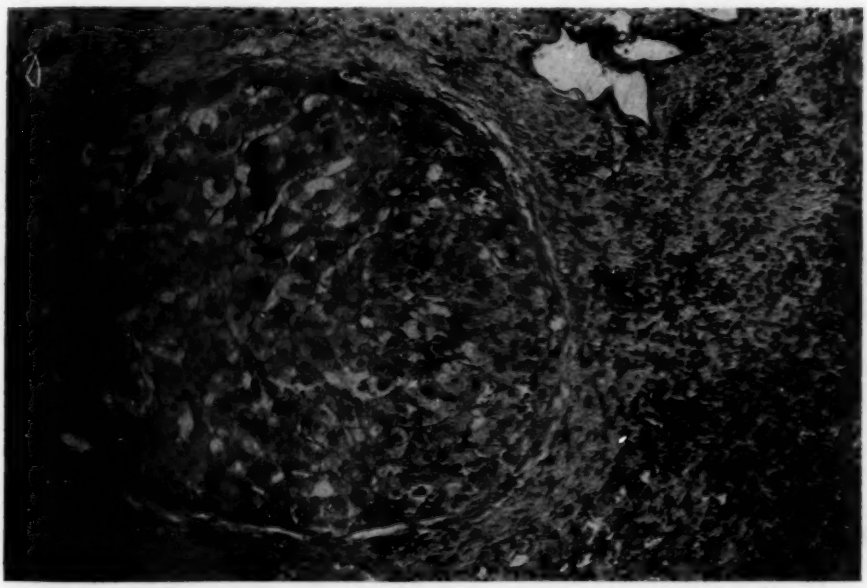

Fig. 4.—Advanced tuberculosis of the suprarenal gland with hypertrophic cortical adenoma remaining; × 150.

work, stated that he had never seen evidence of healed tuberculous lesions in the suprarenal glands. It would appear that the tuberculous process is always progressive until the gland is almost completely destroyed.

Atrophy.—The remaining three of the twenty-eight cases of Addison's disease which were studied had advanced atrophy of the suprarenal glands.

In case 9, the glands were similar and were very small. Histologic study of sections of these showed that the medulla was fairly normal

19. Robertson, H. E.: Personal communication to the author.

but that the cortex was reduced to a narrow strip. Under higher magnification the cortex was found to consist of isolated cortical cells and groups of cortical cells; all of these cells were large, deeply stained and pigmented and contained large, dark nuclei which varied much in size. Between the cells were numerous lymphocytes throughout the cortical layers, and on the margins were numerous fibroblasts (fig. 5). The whole gland was surrounded by a rather thick capsule of fibrous tissue. In a few places in the cortex, and in the fat around the cortex, there were areas of recent hemorrhage. This is similar to the condition in Brenner's third case.

The picture was difficult to interpret. There was unquestionably a chronic inflammatory reaction in the suprarenal cortex, and the reaction

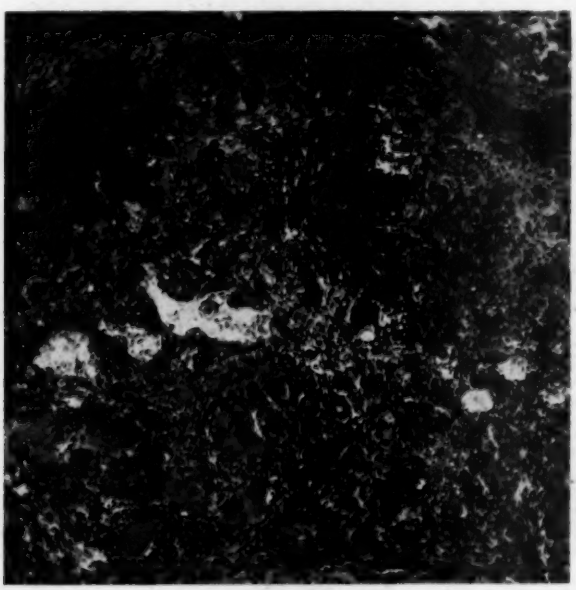

Fig. 5.—Advanced suprarenal atrophy with hypertrophy of the remaining cortical cells and inflammatory reaction of an unknown cause; × 150.

was more or less restricted to the cortex. There was no histologic evidence of tuberculosis. The great reduction in the thickness of the cortex, the small number of cells remaining, their isolation and their marked hypertrophy, however, suggest that some toxic agent was destroying the cortical cells and that the inflammatory reaction was provoked by the destroyed cells. That primary hemorrhage had taken place is possible but the diffuseness and bilaterality of the lesion, as well as the absence of blood pigment, are against this. The condition is probably best considered, as Brenner believes, as primary toxic atrophy or as a low grade inflammatory process of unknown cause.

In case 13, one suprarenal gland was found to be a solid calcified mass about the size of a normal gland. The only remains of the other gland were found to be two small nodules of rather dark colored tissue, each about 5 mm. in diameter. Histologically, these consisted of deeply pigmented medullary tissue with a narrow margin of normal size but deeply pigmented cortical cells. The patient in this case had had cutaneous pigmentation but this had cleared up some time before death. Also, this patient had had a positive Wassermann reaction of the blood and a history of syphilis and intensive treatment. The calcified mass may have been tuberculous, but this cannot be proved. The part played by syphilis is doubtful.

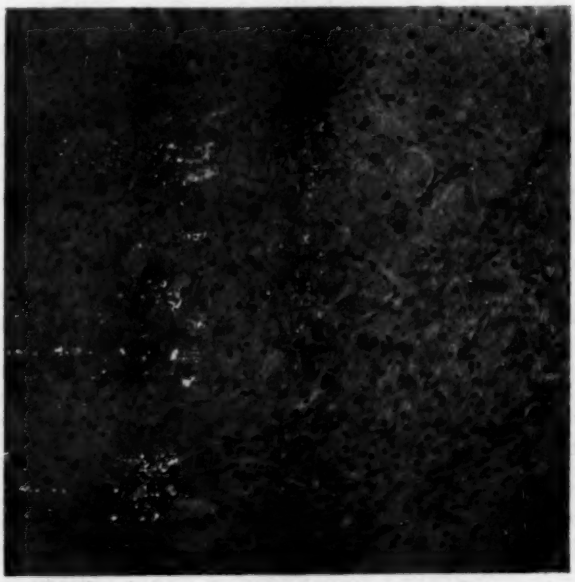

Fig. 6.—Advanced suprarenal atrophy with attempts at hypertrophy and regeneration of the cortical cells; × 150.

Several cases are reported in the literature in which there was tuberculous destruction of one suprarenal gland and atrophy of the other. One possible explanation of the sequence of events in case 13 is that several years before death one suprarenal gland had been destroyed and had become calcified without any addisonian symptoms being manifest. Then active syphilis or some other toxic process had caused atrophy of the other suprarenal gland and pigmentation had developed. The atrophy was then arrested either spontaneously or by antisyphilitic treatment; the remnant of the atrophied gland regenerated, and the pigmentation disappeared.

In case 25, the two glands were similar. They were dark brown, nodular and weighed 0.9 and 1.2 Gm., respectively. Histologic study of sections revealed marked diminution in the amount of both cortex and medulla; the latter apparently had been more affected. The cortex was composed mostly of nodules, which under low power magnification resembled a cluster of cortical adenomas. Under higher magnification, marked alterations in the cortical cells were observed. These varied tremendously in size; many were very large, with poorly staining cytoplasm, in which there was a moderate amount of pale brown pigment. The nuclei also varied in size and stained deeply. The cells were not arranged in any discernible order. The general appearance suggested that there was a striking reduction in the number of cortical cells and that those remaining had undergone compensatory hypertrophy (fig. 6). There was no evidence of any acute or chronic inflammatory process in either gland. This condition corresponds to that of the suprarenal glands in the case reported by Kiefer.

LESIONS OTHER THAN THOSE OF THE SUPRARENAL GLANDS

Although the syndrome of Addison's disease has long been associated with extensive lesions of the suprarenal glands, changes in other organs should not be neglected, and I have tried so far as possible to secure and tabulate all the available necropsy data on the twenty-eight cases presented in order to determine what other lesions were present often enough to appear significant.

Active Tuberculous Lesions.—One of the first questions that arises in cases of suprarenal tuberculosis is concerned with the association of healed or active tuberculous lesions of other parts of the body; the answer to this question might throw some light on the portal of entry and the question of specificity of the organisms. Other writers on the subject frequently have found both healed and active lesions of other organs associated with Addison's disease. In all of the twenty-five cases of tuberculosis of the suprarenal glands in this series there were lesions that were considered to be those of healed pulmonary tuberculosis; these consisted of calcified nodules in the lungs and lymph nodes of the hilum, and pleural adhesions. In all there were at least two of these three types. In addition, in six cases were what appeared to be healed lesions of tuberculosis in at least one of the following sites: the spleen, the liver, the peritoneum and the joints. It is well known that the incidence of healed pulmonary tuberculosis is high, as determined by the routine of necropsy examinations, but that it is rarely as high as 100 per cent in any group of twenty-five cases. In one of the three cases in which there was atrophy of the suprarenal glands (case 25) a demonstrable healed or active tuberculous process was not found. Data concerning active tuberculosis are given in table 2.

TABLE 2.—*Summary of Pathologic Anatomy of Organs Other Than Suprarenal Glands*

Case	Active Tuberculous Lesions Other Than Those of the Suprarenal Glands	Body Weight		Weight of Heart				Condition of Kidneys	Hyperplasia		Intestinal Lymphoid Tissue
				At Necropsy	Computed Normal				Thymus, Grade	Lymph Nodes, Grade	
		Pounds	Kg.		Minimal	Average	Maximal				
1	Miliary of liver	...	..	...	...	...	...	Normal	?	..	
2	Apexes of both lungs	...	..	...	...	...	...	Moderate congestion	?	1	Appendix, graded 2
3	Left lung and nodes of hilum	105	47	188	165	205	241	Chronic pyelonephritis	?	1	
4	Miliary of liver and spleen	...	..	...	...	...	...	Normal	?	..	
5	Abdominal lymph nodes	...	..	...	...	...	...	Diffuse tubular atrophy	?	2	
6	Right lung; right tuberculous empyema	140	63	240	211	253	295	Diffuse tubular atrophy	..	..	
7	Mesenteric lymph nodes	120	54	300	190	235	276	Moderate congestion	?	2	Ileum, graded 2
8	Both lungs; both kidneys; prostate; left testis; epididymis and seminal vesicles; rectum; miliary of spleen, and abdominal lymph nodes	...	..	...	...	...	...	Bilateral tuberculosis	3	2	Jejunum, ileum and colon, graded 2
9	None found	152	69	283	240	300	350	Marked congestion	2	2	Jejunum, ileum, colon and appendix, graded 2
10	Both lungs and lymph nodes of hilum; miliary of myocardium, abdominal lymph nodes and spleen	150	68	214	237	294	345	Diffuse tubular atrophy and marked congestion	..	1	Ileum and jejunum, graded 2
11	Both lungs; prostate; left testis and epididymis; first and second lumbar vertebrae	105	47	189	165	205	241	Moderate congestion	2	2	Colon, graded 2
12	Abdominal lymph nodes	140	63	297	221	274	322	Diffuse tubular atrophy	..	..	
13	None found	150	68	238	237	294	345	Diffuse tubular atrophy and moderate congestion	1	..	Colon, graded 2
14	Left kidney; spleen; abdominal lymph nodes	145	65	310	229	284	333	Left tuberculosis; right normal	1	1	Duodenum, ileum and colon, graded 2
15	Both lungs (small nodules)	185	83	292	296	363	382	Normal	..	1	Appendix, graded 2
16	Right lung (small nodules)	170	77	205	255	306	343	Chronic pyelonephritis	.	2	Cecum, graded 2
17	None found	91	41	152	136	164	195	Diffuse tubular atrophy	2	2	
18	Right kidney; prostate; epididymis; seminal vesicles, abdominal lymph nodes	170	77	345	238	333	371	Right tuberculosis; left normal	1	2	Jejunum and ileum, graded 2
19	Both kidneys; prostate; abdominal lymph nodes	...	..	...	...	...	...	Bilateral tuberculosis	..	..	
20	None found	...	..	...	...	...	...	Normal	?	?	?
21	Prostate; left epididymis; left axillary lymph nodes	161	73	235	254	314	369	Moderate congestion	..	..	
22	None found	...	..	...	...	...	...	Diffuse tubular atrophy and moderate congestion	?	?	?
23	Both lungs	135	60	205	213	265	310	Normal	..	1	
24	Both lungs; lymph nodes of hilum and trachea	143	64	246	225	280	328	Normal	2	2	
25	None found	133	59	263	210	260	305	Moderate congestion	3	3	Jejunum, ileum and colon, graded 3
26	Both lungs (small nodules)	145	65	220	229	284	333	Normal	3	2	
27	Both lungs; pleura; mediastinum; fourth, fifth and sixth thoracic vertebrae; fourth, fifth and sixth right ribs	150	68	339	237	294	345	Diffuse tubular atrophy	..	..	
28	Tenth and eleventh thoracic vertebrae with large left psoas abscess; liver	120	54	200	180	215	259	Marked diffuse tubular atrophy	..	2	Ileum, graded 2

Of the twenty-five cases of suprarenal tuberculosis, in ten there was active pulmonary (without genito-urinary) tuberculosis, in four there was active genito-urinary (without pulmonary) tuberculosis, in two there was both active pulmonary and genito-urinary tuberculosis and in one case there was active tuberculosis of the spine without pulmonary or genito-urinary tuberculosis, all of which I believe probably antedated the suprarenal tuberculosis. In three of the remaining eight cases, active tuberculosis of other organs was not found. In the other five cases there was active tuberculosis of the liver, spleen or abdominal lymph nodes, all of which can probably best be considered as coincidental or secondary to the suprarenal tuberculosis. Active tuberculosis was not found in the three cases in which there was atrophy of the suprarenal glands.

Disproportions Between Cardiac and Body Weight.—A small heart and small aorta have frequently been described in Addison's disease and have been considered as due to atrophy secondary to the disease itself, particularly to the hypotension and circulatory weakness, or as a part of a sort of congenital status thymicolymphaticus which will be discussed later. In my series there is a record of the weight of the heart in twenty of the twenty-eight cases. With the use of the table of average normal weights of hearts with upper and lower limits as worked out by Smith [20] from total body weights, a comparison of the computed normal weights with the actual weights of the hearts in these twenty cases is given in table 2. The body weights were taken within a few weeks before death, as were Smith's.

The essential facts can best be summarized as follows: The weight of the heart was more than 25 Gm. below the minimal normal in one case, less than 25 Gm. below the minimal normal in six cases, within normal limits but less than the average normal in seven cases, within normal limits but more than the average normal in five cases, and greater than maximal normal in one case; the weight of the heart was thus less than the average normal in fourteen cases and greater than the average normal in six cases.

In this group of twenty cases, all the patients stated as their normal weight a figure higher than that found within a few weeks of their death. The loss in weight varied between 5 and 70 pounds (2.3 and 31.8 Kg.), with an average of 28 pounds (12.7 Kg.). A summary of a comparison of the weights of their hearts at necropsy with the normal weight of the heart in each case as computed from their normal body weight by the method described is as follows: The weight of the heart was more than 25 Gm. below the minimal normal in seven cases, less than 25 Gm. below the minimal normal in four cases, within normal

20. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79, 1928.

limits but less than the average normal in seven cases, and within normal limits but more than average normal in two cases; the weight of the heart was thus less than the average normal in eighteen cases and greater than the average normal in two cases. The significance of the calculations just enumerated is questionable since a certain amount of atrophy of the heart may be expected from a loss of weight due to any cause.

Significant changes were not noted in the size of the aorta in this series except that the circumference at the valve and in the ascending aorta was roughly proportional to the weight of the heart.

Renal Lesions.—The frequent presence of albuminuria and terminal renal insufficiency in cases of Addison's disease has raised the question as to whether there is a diffuse renal lesion. In table 2 are given the observations relating to the condition of the kidneys in the series. The essential facts displayed in table 2 in regard to the condition of the kidney are as follows: The kidneys were normal in seven cases, congestion was present in six cases, diffuse tubular atrophy in six cases, congestion and diffuse tubular atrophy in three cases, chronic pyelonephritis in two cases and renal tuberculosis in four cases.

The tubular atrophy mentioned consisted in a flattening out of the epithelial cells, with definite diminution in the amount of cytoplasm. In most of these cases the tubules appeared small in diameter and there was intertubular edema. In several of the cases there was fat in the tubular cells. This picture is interpreted as that of a definite degenerative renal lesion or toxic nephrosis, and its presence in nearly a third of the cases seems significant. It is possible that it is the result of low blood pressure and anoxemia or that it is the result of the peculiar terminal toxemia, the mechanism of which is as yet poorly understood.

Hyperplasia of Lymphoid Tissue.—The question of status thymicolymphaticus as a predisposing factor or as a concomitant manifestation in Addison's disease, especially in the cases of atrophy of the suprarenal glands, has been discussed by other authors. In addition to cases in which small hearts were found, a number of cases have been described in which the thymus and lymph nodes were enlarged and in which there was hyperplasia of the lymphoid elements in the small and large intestines. A summary of these data in my series is presented in table 2.

It will be noted that in all three cases of suprarenal atrophy enlargement of the thymus and intestinal lymphoid tissues had taken place. There was a similar condition in seven of the cases of suprarenal tuberculosis and there were varying degrees of lymphoid hyperplasia in a number of the others. An active tuberculous focus as a cause of diffuse lymphoid hyperplasia cannot be ruled out. Certainly, the incidence of these lesions is high in Addison's disease. The spleen was enlarged

in eight cases; its weight varied from 285 to 470 Gm. The enlargement is of doubtful significance.

Miscellaneous Lesions.—Other lesions which probably were incidental or which are difficult to link up with Addison's disease were as follows: cholelithiasis in five cases, duodenal ulcer in four cases, melanosis coli in three cases, hyperplasia of Brunner's glands in two cases, carcinoma of the stomach in one case and carcinoma of the rectum in one case.

COMMENT

Because of the reports in the literature of cases of Addison's disease in which the suprarenal glands presented other lesions than tuberculosis and atrophy, a study was made of all the suprarenal lesions found at necropsy at The Mayo Clinic during the last eighteen years. None of the patients in these cases had clinical Addison's disease. A brief summary of these cases is given in table 3; the group of seventy-three cases includes two cases of moderate atrophy and the eight cases of early or unilateral tuberculosis, previously mentioned, in which the clinical addisonian syndrome was not observed.

TABLE 3.—*Summary of Lesions of the Suprarenal Glands in Seventy-Three Cases in which Addison's Disease was not Present Clinically* *

	Unilateral Involvement			Bilateral Involvement			
		Estimated Suprarenal Tissue Remaining			Estimated Suprarenal Tissue Remaining		
Suprarenal Lesions	Cases	per Cent	per Cent	Cases	per Cent	per Cent	Primary Disease
Primary carcinoma.....	9	75	50	2	25	10	Carcinoma of suprarenal gland
Primary neurocytoma...	2	50	50	..	..	..	Neurocytoma of suprarenal gland
Primary neuroblastoma	..	..	..	1	15	..	Neuroblastoma of suprarenal gland
Primary paraganglioneuroma	1	50	..	..	..	..	Paraganglioneuroma of suprarenal gland
Sarcomatous invasion...	1	90	..	..	..	..	Retroperitoneal myxosarcoma
Metastatic sarcoma.....	3	90	50	2	50	25	Sarcoma of various organs
Metastatic carcinoma...	17	90	50	16	90	10	Carcinoma of various organs
Moderate atrophy.....	..	..	..	2	50	50	Pituitary tumor and exophthalmic goiter, respectively
Amyloidosis.....	..	..	..	3	60	15	Pulmonary tuberculosis, osteomyelitis of leg and perinephritic abscess, respectively
Infarction.....	1	50	..	1	20	..	Cardiac disease
Hemorrhage.....	..	..	..	3	50	25	Appendicitis, lobar pneumonia and chronic bronchitis, respectively
Abscess.....	..	..	..	1	25	..	Carcinoma of bladder
Tuberculosis.....	4	80	50	4	90	20	Miliary tuberculosis (3 cases); renal tuberculosis (2 cases); cardiac disease (2 cases); spinal tuberculosis (1 case)

* In only ten cases was more than 75 per cent of the suprarenal tissue apparently destroyed.

It will be noted that the minimal approximate amount of suprarenal tissue remaining was 10 per cent. This is interesting since in only one of the cases of tuberculosis with Addison's syndrome (case 12, table 1) apparently as much as 10 per cent of suprarenal tissue remained; in the other cases there was considerably less than this. It has been suggested by others, however, that an inflammatory lesion is much more likely to produce the clinical syndrome than one that is neoplastic. In one case of tuberculosis the amount of destruction was approximately 80 per cent and addisonian symptoms were not present. If it is considered that suprarenal insufficiency is the cause of Addison's disease it would appear that the limit of the margin of safety is reached when somewhere between 80 and 90 per cent of the suprarenal tissue has been destroyed.

Possibly the reasons why neoplastic lesions produce Addison's disease so rarely are that the patient rarely lives long enough to have tumors in both glands and if he does the primary disease or metastasis to other vital organs causes death before the suprarenal tumors have grown large enough to destroy much suprarenal tissue. It is evident that although malignant tumors are invasive, they are not nearly so destructive to highly specialized glandular tissue as is tuberculosis. Amyloidosis as a destructive agent may be considered as acting more like malignant conditions than like tuberculosis. The cases of infarction, hemorrhage and abscess in table 3 apparently were associated with terminal stages of the primary disease. Records of cases of gumma or fatty replacement of the suprarenal glands were not found in the material studied.

SUMMARY

Necropsy data are presented from twenty-eight cases of Addison's disease. Among these, there was bilateral tuberculosis of the suprarenal glands in twenty-five; acid-fast bacilli were demonstrated in eleven of these cases. There was advanced bilateral suprarenal atrophy in three cases. In all the cases but one some suprarenal tissue remained; the maximal amount remaining in any one case was approximately 10 per cent of the normal.

Healed tuberculous lesions of the lungs were found in all the cases in which there was tuberculosis of the suprarenal glands. Active tuberculosis of other organs was found in twenty-two of these. The weight of the heart was less than the average normal in fourteen of twenty cases in which data on the weight of the heart were available. Diffuse degenerative changes in the renal tubules were present in nine cases. In ten cases, including the three cases of suprarenal atrophy, the thymus was enlarged and there was hyperplasia of lymphoid tissue in the nodes and intestinal tract. There was scattered lymphoid hyperplasia in eight other cases.

Seventy-three cases in which there were suprarenal lesions but in which clinical evidence of Addison's disease was lacking are briefly presented. Among these seventy-three cases are included the following: primary suprarenal neoplasms, fifteen cases; secondary suprarenal neoplasms, thirty-nine cases; atrophy, two cases; amyloidosis, three cases; infarction, two cases; hemorrhage, three cases; abscess, one case, and tuberculosis, eight cases.

LATE GROSS LESIONS IN THE AORTA AND PULMONARY ARTERY FOLLOWING RHEUMATIC FEVER *

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The fact that widespread lesions commonly occur in the aorta and the vessels throughout the body during and following rheumatic fever has been definitely established by Pappenheimer and von Glahn [1] in their important extension of the earlier observations of Klotz.[2] Since their publication, numerous observers [3] have added valuable confirmatory data. In almost every instance, however, the vascular lesions described have been microscopic. Recently Kugel and Epstein [4] and Perla and Deutsch [5] have called attention to the gross changes that may occur in acute rheumatic fever in the aorta and the pulmonary artery; Pappenheimer and von Glahn [6] also reported the presence of brownish plaques in one of their cases. We believe that late gross lesions may occur and readily be explained by the occurrence and confluence in a localized area of the small flame-shaped scars which are the microscopic changes characteristically found in the media. We have recently had the opportunity to examine an aneurysm of the aorta in which all the evidence pointed to a rheumatic origin and a pathologic process of this type. This case, which we shall report, prompted us to examine all the hearts available in our laboratory for evidence of gross lesions intermediary between the microscopic scars and the formation of an aneurysm. Unfortunately, few specimens of the aorta, except for limited portions attached to the heart, had been preserved. It is the purpose of this

* Submitted for publication, April 13, 1929.

* From the Department of Pathology of Washington University School of Medicine, and of Barnes Hospital.

1. Pappenheimer, A. M., and von Glahn, W. C.: J. M. Research **44**:489, 1924; Am. J. Path. **2**:15 and 235, 1926; ibid. **3**:583, 1927.

2. Klotz, O.: Tr. A. Am. Phys. **27**:181, 1912.

3. Paul, J. R.: Medicine **7**:383, 1928. Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, Arch. Path. **6**:247 (Aug.) 1928. Chiari, H.: Beitr. z. path. Anat. u. z. allg. Path. **80**:336, 1928. Perla, D., and Deutsch, M.: Am. J. Path. **5**:45, 1929.

4. Kugel and Epstein (footnote 3, second reference).

5. Perla and Deutsch (footnote 3, fourth reference).

6. Pappenheimer and von Glahn (footnte 1, third reference).

paper to report the late gross lesions that were discovered in the aorta and pulmonary artery of the rheumatic hearts examined, and to correlate such lesions, as far as possible, with the known pathologic changes in rheumatic fever. In doing so, we make the reservation, however, that what we know as rheumatic fever awaits the accepted discovery of the causative agent of this disease and the experimental production of its lesions.

In selecting the material, the criteria of Pappenheimer and von Glahn were adopted, namely: (1) a clinical history of one or more attacks of rheumatic fever or of chorea or of repeated attacks of tonsillitis; (2) the presence of the typical lesions of rheumatic fever in the heart, and (3) the absence of syphilis in the history, in the serologic reaction and in the gross or histologic appearance of the aorta and the other organs. In addition, arteriosclerosis and known mycotic processes were considered and ruled out in each case. Three cases besides the one in which aneurysm was shown were found that conformed to these conditions, although three or four others might have been included in this number. Only the essential details will be given in the descriptions of the cases.

REPORT OF CASES

CASE 1.—J. H., a white woman, aged 20, entered Barnes Hospital with heart failure and auricular fibrillation. She gave a history of repeated attacks of tonsillitis and rheumatic fever with arthritis. The Wassermann reaction was negative. The blood pressure was 140 systolic and 85 diastolic. The autopsy, which was limited to the chest, revealed an enlarged heart and chronic tricuspid and mitral endocarditis; the mitral valve being of button-hole type. Six fine, smooth depressions about 1 mm. in diameter gave the pulmonary artery, in an area 3 cm. above its origin, a honeycomb appearance (fig. 1). On section, the intima between the depressions appeared thickened and the media somewhat irregular. The adventitia was wider than normal, containing numerous vessels.

Microscopic Examination.—The intima of the pulmonary artery in places was over one-half as thick as the media (fig. 2). This thickening was produced by an increase in connective tissue, the intima near the lumen being dense and hyaline, and that near the media being more cellular. Only an occasional lymphocyte was seen. The muscle of the media, in a few places, especially beneath the depressions, had disappeared, and its place had been taken by connective tissue (fig. 2). A van Gieson stain for elastic tissue revealed a frayed and slightly broken elastic layer, which in places was pushed aside by small bands of connective tissue. The arteries and veins of the adventitia were thickened, the latter eccentrically.

The small arteries and arterioles of the myocardium, pericardium, auricle, aorta and lung were definitely thickened by hyaline connective tissue.

CASE 2.—J. S., aged 40, a white man, had rheumatic fever at the ages of 12, 22 and 32. The Wassermann reaction was negative on two occasions. The blood pressure was 160 systolic and 120 diastolic. No scar was seen on the penis. Death was caused in this case by heart failure. At postmortem examination, the heart was found to weigh 510 Gm. The mitral valve was stenosed; the aortic and tricuspid valves were definitely fibrosed. The mouth of the left coronary

Fig. 1 (case 1).—Pulmonary artery, showing gross scarring; × 2.

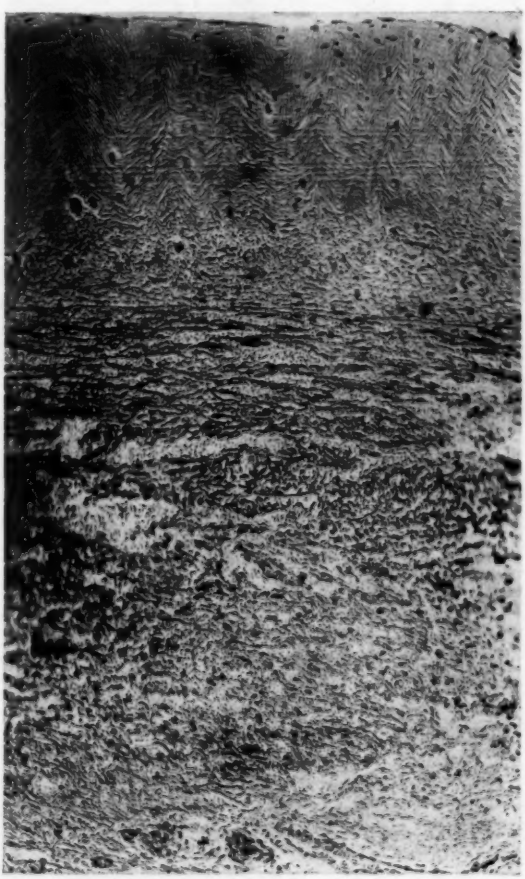

Fig. 2 (case 1).—Hypertrophy of intima. Disappearance of the muscle of media and replacement with scar tissue; × 85.

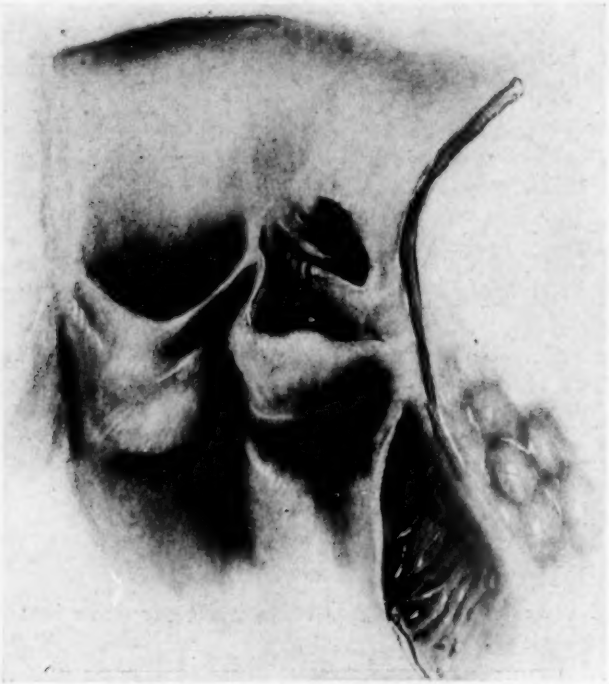

Fig. 3 (case 2).—Scarring of the mouth of the coronary artery.

Fig. 4 (case 2).—Eccentric fibrous thickening of veins. A similar picture was seen in veins in all cases; × 250.

artery was widened, especially on its mesial aspect, where several small scars (fig. 3) gave the opening of the coronary artery a puckered appearance.

Microscopic Examination.—The intima was moderately thickened and contained a small calcified area. The media was partially broken by several scars, some of which had attained a fair size. The adventitia showed changes that were found in all the cases: increase in connective tissue, chiefly hyaline; thickening of the small arteries and arterioles, and eccentric thickening of the veins (fig. 4).

The connective tissue was increased about the vessels of the myocardium. There were several small scars that showed no definite perivascular arrangement. The small arteries and arterioles of the kidneys, intestines, prostate, spleen and suprarenal glands were thickened.

Fig. 5 (case 3).—Large scar in upper part of aorta. Stippled appearance in lower part of aorta caused by numerous small scars in media.

Case 3.—J. G., a white man, aged 47, entered Barnes Hospital with all the signs and symptoms of heart failure. He denied having had any childhood disease, rheumatic fever, chorea or syphilis. He had always been susceptible to colds. He had had "water on the chest" at varying intervals since he was 7 years old. The physical examination revealed ragged, scarred tonsils, aortic insufficiency and mitral stenosis. The Wassermann reaction was negative on three occasions. The blood pressure was 120 systolic and 80 diastolic. No scar was found on the penis.

Grossly, the aorta, 8 cm. above the aortic valve, showed a linear scar about 1.5 cm. in length, with a smooth, thickened intima surrounding it (fig. 5). On section, the media was found to be decreased in the region of the depression; the

Fig. 6 (case 3).—Scar in media, showing destruction of media. Slight cellular reaction; × 85.

Fig. 7 (case 3).—Fibrous thickening of small artery; × 213.

intima and adventitia were thickened. Immediately above the aortic valve, the intima of the aorta was given a stippled appearance by numerous fine depressions. On section, the intima was seen to be irregularly thickened; the media was found to contain many small red points. The aortic and mitral valves were markedly fibrosed, the latter valve presenting a mere slit as its opening. The heart was enlarged.

Microscopic Examination.—The media tapered down to a thin layer at the site of the large gross scar, whereas the intima and adventitia were considerably thickened. The numerous scars in the media are illustrated in figure 6. The muscle and elastic tissues were broken by the vascularized connective tissue, in which only occasional lymphocytes were noted. The adventitia consisted of a

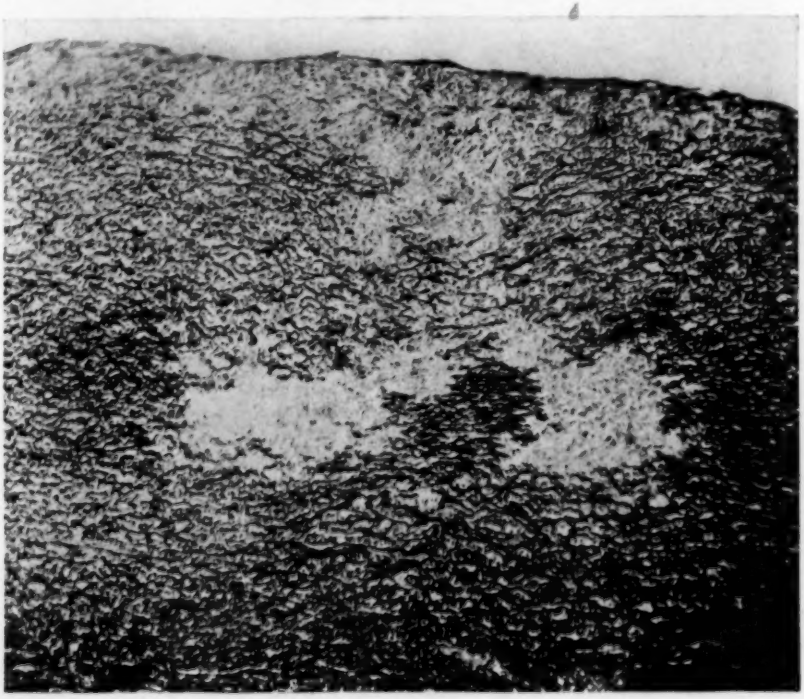

Fig. 8 (case 3).—Elastic tissue (van Gieson stain), showing scar in media; × 90.

broad layer of hyalinized connective tissue, in which many thickened vessels, such as the one illustrated in figure 7, were prominent. The increased thickness of the walls of these vessels was found by a van Gieson stain for elastic tissue to be due to hyaline connective tissue in the media. Several small accumulations of lymphocytes were located in the lowermost portions of the connective tissue. The thickened intima consisted of a somewhat loose connective tissue and a few lymphocytes. This thickening of the intima together with small scars beneath the depressions accounted for the stippled appearance in the lower part of the aorta.

The aorta adjacent to these regions and elsewhere revealed a media that was changed by small scars, figure 8, and an adventitia that was increased in width

by hyaline connective tissue in which were thickened small arteries and arterioles. Many of the small veins of the aorta throughout the various sections of the aorta showed eccentric thickening by either cellular or dense connective tissue (similar to that illustrated in fig. 4).

The perivascular connective tissue of the myocardium was increased. The small arteries and arterioles of the myocardium, pericardium, lungs, liver, pancreas, peripancreatic fat, kidneys, suprarenal glands, prostate and spleen were thickened in a mild degree.

Fig. 9 (case 4).—An aneurysm of the aorta of dissecting type. The small opening of the aneurysm and the smoothness of the aorta may be noted.

CASE 4.—P. F., a white man, aged 39, a salesman, was admitted to Barnes Hospital for dyspnea and marked palpitation of the heart. At the ages of 23 and 25, he had had severe attacks of rheumatic fever with involvement of the joints. He denied having had a chancre. He was married and had two children, who were alive and well. Miscarriages, stillbirths or other signs of syphilis were absent in the history. For the past four years he had been having palpitations, which, he was told, were due to a "leaky heart." Dyspnea had been pronounced for three weeks.

The physical examination revealed an orthopneic and dyspneic person with external cyanosis of the lips and fingers. Cardiac decompensation was evident. Blood culture and Wassermann and Kahn tests of the blood were negative. The

blood pressure was 82 systolic and 68 diastolic. The clinical course was rapidly downhill. The patient died of cardiac failure.

Autopsy.—At autopsy, an aneurysm of the aorta was seen above and partially attached to the right auricle, arising from the ascending portion of the arch of the aorta. On section, this aneurysm was found to be unusual (fig. 9). The laminated thrombus of the aneurysm was in communication with the aorta at a point 2 cm. above the aortic valve through a smooth, round opening, 1 cm. in diameter. The main mass, which measured 8 by 7 by 5 cm., was covered posteriorly by the wall of the aorta, which, however, did not consist of more than the intima and about half of the media. The upper angle of the aneurysm

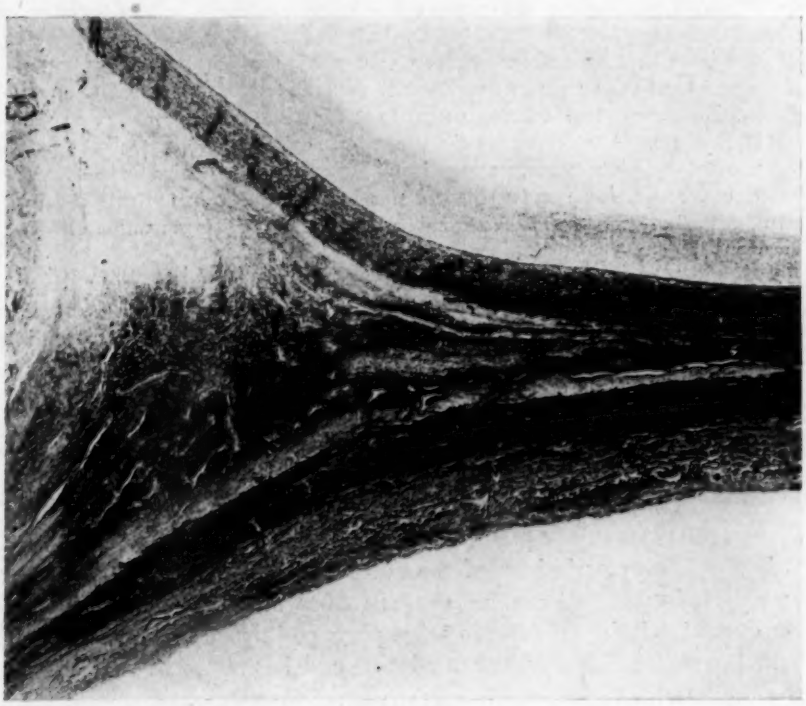

Fig. 10 (case 4).—The upper edge of the aneurysm, showing the dissection of the aorta. Connective tissue binds the two halves of the aorta. Several small scars are seen in the adventitial half of the media. Elastic tissue shown by van Gieson stain.

showed the media split in two so that part of the media was a direct extension of the posterior surface just described, while the other part formed the anterior upper wall of the aneurysm. The remainder of the anterior wall consisted of dense hyaline connective tissue and the adherent right auricle. The aortic wall below the opening did not show this dissecting process. The aneurysm extended down to about the line of attachment of the aortic valve. The intima, except for the opening, was smooth; no scarring was found, and only a few small atheromas were noticed. The cusps of the aortic valve were thick, short and retracted, the anterior and right posterior cusps being fused; and at this point calcium was felt.

Otherwise, the thickening was fibrous. The aorta above the cusps did not show any change. The mitral valve was thickened, especially the anterior leaflet, where a few of the chordae tendineae were shortened and thickened.

Microscopic Examination.—Around the opening in the aorta, muscle and elastic tissue were intermingled with connective tissue, which extended into and covered the thrombus for a short distance. In either direction away from the opening, the muscular elastic coat was not broken. The portion of the aorta that formed the posterior wall of the aneurysm consisted of an intima that was increased by connective tissue, and a media that was thin, but contained unbroken muscle and elastic tissue and a layer of fairly cellular connective tissue. This was separated from the thrombotic mass by dense hyaline connective tissue. The split in the media, at the upper angle of the aneurysm, was held together by connective tissue (fig. 10). The portion of the aorta here that still remained as part of the aorta showed no change, that portion which formed the anterior upper surface of the aneurysm was the site of numerous small vascularized scars with a thickened fibrosed adventitia next to it (fig. 10). No lymphocytic reaction was found here. A section through the middle of the anterior surface of the aneurysm at a point farthest away from the aorta revealed a dense layer of hyaline connective tissue and a few strands of broken elastic tissue. The latter was next to the thrombus. The thrombus was undergoing organization only near the aorta itself.

Several sections were taken through the aorta away from the aneurysm, two of them beneath atheromas. One of the sections beneath an atheroma showed a thinned media in which the lower half was partially replaced by several scars. The adventitia at and adjacent to this point was thickened. Throughout the adventitia in all parts of the aorta the arterioles and veins were thickened, the thickening in the latter usually being eccentric. Many arterioles of the heart and an occasional vessel of the other organs showed slight thickening. There were several small scars in the heart situated chiefly about the vessels.

COMMENT

These late gross lesions of the aorta and the pulmonary artery can readily be interpreted as the sequelae of previous rheumatic lesions. The excessive intimal thickening that plays so important a rôle in case 1 is the late result of the gross acute lesion that has already been described by Perla and Deutsch. In their paper, figure 7 pictures an intimal change that in extensiveness and time is only slightly removed from the intimal change in case 1.

It is somewhat difficult to decide on the etiologic mechanism in the production of this intimal change. The constant presence of medial change and the widespread involvement of the vessels tend to favor the view that the infective agent is brought by way of the vasa vasorum rather than through the lumen of the aorta or the pulmonary artery. If this is true, we must emphasize the possibility of marked injury to the intima with moderate involvement of the media, the adventitia and the vasa vasorum.

Although in the European literature one reads many accounts of the destructive effects of rheumatic fever on the aorta, few of these

accounts offer definite histologic evidence. Recently Wiesel [7] and Besançon and Weil [8] have emphasized the serious involvement of the aorta. From the known pathologic changes in rheumatic fever and from our studies, we can understand how gross lesions and even the formation of an aneurysm may be the sequelae of rheumatic fever. The mechanism for the production of these lesions may be predicated from the changes that have been found in rheumatic fever and accepted as being due to that disease. Should the acute reaction that is described as the forerunner of the flame-shaped scars be a little more extensive or should several of these lesions be localized in one area, the resulting healing process may well terminate in a gross scar; or should the reaction take place within a wall of the vasa vasorum with a subsequent thrombosis of that vessel, gross scarring may result. We have seen this latter process in its acute stage in the coronary artery and in the branches of the pulmonary artery. We have seen the apex of the heart [9] markedly thinned and slightly bulging in rheumatic fever. This was thought to be due to the late results of a coronary thrombus caused by rheumatic fever. The large scars that we sometimes see in the kidneys and spleen, that resemble healed infarcts, are probably due to thrombosis of the vessels of these organs in patients who have had rheumatic fever. The rarity of these gross lesions in the aorta may be attributed either to the relatively slight involvement of the aorta in rheumatic fever or to the belief that because the scars of the media resemble a process produced by syphilis it is a syphilitic process. Aside from the history, the clinical picture, the serologic tests and the observations in the other parts of the body, there are definite histologic differences between the scars of the media in syphilis and the scars found in these cases that we believe are due to rheumatic fever.

The gross scarring was confined to one small area, except in case 3, in which two localities had undergone change. In none of the regions of the scars did we find more than a few lymphocytes. This fits in well with the late lesions of rheumatic fever in the heart valves and the myocardium, and the descriptions of the aortic lesions by Pappenheimer and von Glahn. It would indeed be unbelievably rare to find four cases in which the Wassermann and Kahn tests were negative, in which there had been no history of or treatment for syphilis and in which there was unquestioned rheumatic involvement, which would show what might be considered an atypical syphilitic aortitis. The changes in the smaller arteries and veins in no instance consisted of the intimal proliferation that one so frequently sees in syphilis. When the vessels were thickened, we usually found an increase in connective tissue within the wall of the

7. Wiesel, J.: Med. Klin. **19**:197, 1923.
8. Besançon, K., and Weil, M. D.: Lancet **1**:1002, 1928.
9. McCordock, H. A., to be published.

vessel and not an increase in the intima of the vessel. The eccentric thickening of the veins by connective tissue probably is the late stage of an acute reaction that Chiari [10] described as occurring in rheumatic fever. The increase in connective tissue in the adventitia with little lymphocytic reaction in these cases is not confined to the areas of destruction in the media, but is rather diffuse. This, too, was emphasized by Chiari.

The formation of the aneurysm may be plausibly explained on the basis of the changes in rheumatic fever. The aneurysm appears to be the result of a break in the aorta with a subsequent dissection of the aorta along the lower part of the media. The aorta everywhere else was smooth and showed no gross scars and few atheromas. It was this condition that first drew our attention to the fact that here we had an aneurysm that was obviously not syphilitic nor arteriosclerotic nor mycotic. The rupture through the aorta probably occurred at the site of a localized medial destruction similar to the process that produced the gross lesions in cases 2 and 3. The thickened adventitia and lower part of the media held the aorta intact. The lesions in the outer half of the media, to reason from the work of others and the appearance of the aorta at the upper angle of the aneurysm in this case, offered a line of weak points along which the aortic wall could be dissected by the constant force of the blood. This process must have been somewhat slow, because at the farthest point of dissection the split media was held together by well formed connective tissue which appeared to be resisting the advancement of the blood. The formation of a thrombus and the narrowness of the opening were other factors in the probable slow growth of this aneurysm. We found small scars similar to those described in rheumatic fever in the lower part of the media in other parts of the aorta. The rather large medial scar which was found beneath one of the atheromatous plaques was similar to the lesions seen in the other cases, but as yet was too small to be visible grossly. The atheromatous plaque over the site of the thinning of the media was interpreted as being of the nature of a compensatory thickening. There was nothing in the gross or microscopic studies that even suggested an arteriosclerotic or a known mycotic origin for the aneurysm.

The histories in all cases, except case 3, showed definitely the presence of rheumatism. Case 3 belonged to the small group of patients who showed physical and postmortem signs of rheumatic nature, but who gave no history of involvement of the joints or the heart. One should note with interest that this patient as a child had several attacks of what probably was pleurisy. Paul [11] emphasized the frequency and specificity of pleurisy in rheumatic fever.

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10. Chiari (footnote 3, third reference).
11. Paul (footnote 3, first reference).

It might be worth while to mention briefly that in two of the four cases there was hypertension. Gray and Rabinovitch, in this laboratory, are studying the peripheral vessels in the organs of patients with rheumatic fever to determine whether the hypertension which is not uncommon in this disease might not be due to the change in the vessels which results from rheumatic fever.

In our comment, the term rheumatic fever has been used in the sense that the lesions described were not of syphilitic, arteriosclerotic, degenerative mesaortitis or known mycotic origin; the term rheumatic fever has been used rather in the sense that there is a large group of cases that show pathologic changes which, for the most part, probably had their origin definitely in rheumatic fever.

Future study may reveal that there are different organisms, perhaps similar in nature, that directly or through previous sensitization of certain tissues produce lesions that are similar in appearance.

SUMMARY

Four cases are described in which gross lesions of the aorta and pulmonary artery are thought to have been late results of rheumatic changes. These lesions consisted in scarring of the media and thickening of the intima. A false aneurysm of the aorta is described and explained on a rheumatic basis. An eccentric fibrosis of the veins of the adventitia is emphasized as being rheumatic.

We are indebted to Dr. D. P. Ban for the use of the case histories.

THE RÔLE OF CLASMATOCYTES IN PROTECTION AGAINST THE PNEUMOCOCCUS *

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In recent years particular emphasis has been placed on the relationship between the reticulo-endothelial system of cells (as defined by Aschoff [1]) and immunity. In the reticulo-endothelial system have been included mononuclears, namely, the monocytes of the blood, the clasmatocytes (histiocytes, tissue macrophages) of the connective tissue, the endothelial cells of the capillaries and the Küpffer cells of the liver. Many have held that mononuclear as well as polymorphonuclear cells are concerned in active phagocytic opposition to certain infectious agents.

The importance of the vascular endothelium in the disposal of bacteria has been emphasized by various workers, among whom are Werigo,[2] Adami, Abbott and Nicholson,[3] Kyes [4] and Nagao.[5] Bull,[6] Hopkins and Parker [7] and Louros and Scheyer [8] observed the disappearance of streptococci from the blood stream of animals and their presence in the organs. Bartlett and Ozaki [9] observed marked phagocytosis of staphylococci in blood cells, in the capillaries of the lungs, liver and spleen, the mononuclears playing an important rôle. In a perfusion experiment, Manwaring and Coe [10] demonstrated the adherence of the pneumococci to the endothelial cells lining the hepatic capillaries. Singer and Adler,[11] Robertson and his collaborators,[12] and Wright,[13] after immunization with pneumococci, noted marked phagocytosis by both polymorpho-

* Submitted for publication, April 13, 1929.

* From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

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3. Adami, Abbott and Nicholson: J. Exper. Med. **4**:349, 1899.
4. Kyes, P.: J. Infect. Dis. **18**:277, 1916.
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8. Louros, N., and Scheyer, H. E.: Ztschr. f. d. ges. exper. Med. **52**:291, 1926.
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11. Singer, E., and Adler, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **41**:418 and 468, 1924.
12. Robertson, O. H.; Woo, S. T.; Cheer, S. N., and King, L. P.: J. Exper. Med. **47**:317, 1928.
13. Wright, H. D.: J. Path. & Bact. **30**:185, 1927.

nuclear and mononuclear leukocytes in the lungs and liver, and by the Küpffer cells of the liver coincident with the reduction of the number of organisms in the blood stream.

That clasmatocytes play an important rôle in freeing the normal peritoneum from bacteria has been indicated by Jelin,[14] Jensen,[15] Noetzel,[16] Beattie,[17] Buxton and Torrey.[18] Bordet,[19] Wallgren [20] and Kanai [21] observed that the mononuclears played the most important part in the destruction of streptococcus in the blood stream and in the peritoneal cavity.

Gay and his collaborators have shown that there is a definite and constant correlation between accumulation of macrophages (clasmatocytes) and resistance to streptococcus infection in the pleural cavity of rabbits (Gay and Morrison,[22] Gay and Clark,[23] Gay, Clark and Linton [24]). They observed that injection of various substances, such as aleuronat-starch and gum arabic-broth, into the pleural cavity in from eighteen to twenty-four hours produced an exudate predominantly polymorphonuclear and in seventy-two hours one predominantly mononuclear. When the cavity had been prepared seventy-two hours previously, animals were protected against many times the fatal dose of streptococcus "H" injected intrapleurally. The walls were thickened and filled with granulation tissue, and many of the cells were clasmatocytes in which streptococci could be observed undergoing destruction. The animals were not protected against infection in a cavity prepared eighteen hours previously in which the pleural walls were filled almost exclusively with polymorphonuclear cells. The streptococci are phagocytosed both in the exudate and in the tissues almost exclusively by the mononuclear cells; phagocytosis by the polymorphonuclear cells is negligible. These studies show the remarkable protective value of the mobilization of macrophages against local streptococcus infections. Recently it has been shown that after collection of macrophages in one area they may be remobilized in other areas and afford some degree of protection (Gay, Clark and Linton,[24] Linton [25]).

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Bass [26] injected streptococci into the pleural cavity of a normal and of an immunized rabbit and into a twenty-four hour broth prepared cavity, and noted that both polymorphonuclear and mononuclear cells were phagocytic. The phagocytosis was increased with immunization, and only then was the infection localized. He also injected streptococci into the bone-marrow of normal and immunized rabbits, and observed their phagocytosis almost entirely by the histiocytes.

The rôle of the accumulation of tissue macrophages (clasmatocytes) in local infections with organisms other than streptococcus has been observed by a number of workers. Granulating wounds of rabbits were found resistant to staphylococcus and streptococcus but not to *Spirochaeta pallida* and *Pasteurella avicida* (Halley, Chesney and Dresel [27]). The accumulation of macrophages by intracutaneous injections of India ink afforded protection against the streptococcus but not against anthrax or diphtheria (Ledingham [28]). The injection of chemical irritants into the ears of rabbits protected them against the streptococcus but not against anthrax, diphtheria, or the pneumococcus (Cobbett and Melsome [29]). Nakahara [30] prepared the peritoneum of mice with olive oil and found that there occurred, coincident with the increase of macrophages, a local resistance to fatal doses of staphylococcus and pneumococcus as well as a quicker disposal of *B. coli.*

With a number of micro-organisms there appears to be no constant correlation between accumulation of macrophages and resistance to infections. There are conflicting reports in regard to protection against pneumococcus infections. Nakahara [30] obtained protection in the prepared peritoneum of mice. Singer and Adler [31] obtained protection against pneumococcus type III only in prepared pleural cavities of immunized rabbits. Tudoranu [32] obtained protection against pneumococcus III in prepared peritoneal cavities of rabbits only when immune serum was given. He observed phagocytosis by the exudate cells (mostly macrophages) only in the rabbits that had received immune serum. Recently it was found by Stuppy, Cannon and Falk [33] that after

26. Bass, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **42**:269, 1925.

27. Halley, C. R. L.; Chesney, A. M., and Dresel, I.: Bull. Johns Hopkins Hosp. **41**:191, 1927.

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30. Nakahara, W.: J. Exper. Med. **42**:201, 1925.

31. Singer and Adler (footnote 11, first reference).

32. Tudoranu, G.: Ann. de l'inst. Pasteur **40**:606, 1926.

33. Stuppy, G. W.; Cannon, P. R., and Falk, I. S.: Proc. Soc. Exper. Biol. & Med. **36**:314, 1928.

vaccination in the upper respiratory tract of rabbits, the local immunity in the lungs was associated with an accumulation of histiocytes.

On account of these apparent irregularities in resistance to pneumococcus infections shown by these workers and in view of the fact that the studies of Gay and his collaborators have shown that the mobilization of macrophages plays an important rôle in enhanced resistance to streptococcus infections in the pleural cavities of rabbits, it was suggested that a similar study of pneumococcus infections would be of interest. The following series of experiments were undertaken to ascertain what effect accumulation of clasmatocytes had on resistance to the pneumococcus.

INJECTION OF PNEUMOCOCCUS INTO PREPARED PLEURAL CAVITIES OF RABBITS

Technic.—A virulent strain[34] of pneumococcus type I was used for the infection of the pleural cavities of rabbits. Less than 0.0000001 cc. of an eighteen hour blood infusion-broth culture intrapleurally was a fatal dose. The virulence of successive cultures was tested from time to time by the intrapleural route. The pleural fluid of rabbits dying with pneumococcus pleurisy was removed and kept on ice. Rabbit blood infusion-broth cultures were made from the pleural fluid when needed and diluted in broth. A pleural fluid which had been kept for more than from three to four weeks was seldom used. Broth dilutions of from eighteen to twenty-four hour cultures were injected intrapleurally in 1 cc. amounts, and 1 cc. of several of the higher dilutions was plated out in rabbit blood, 0.2 per cent, dextrose infusion-agar and incubated forty-eight hours for the determination of the number of organisms injected.

The cells were mobilized in the pleural cavities of rabbits by injections of aleuronat-starch or gum arabic-broth. The resistance of the cavity was tested by the injection of the pneumococcus at either eighteen or seventy-two hour intervals after preparation.

Injection of Pneumococcus into Seventy-Two Hour Prepared Pleural Cavity.—Experiment 1.—Five cubic centimeters of 5 per cent aleuronat and 3 per cent starch in physiologic solution of sodium chloride was injected into the pleural cavities of four rabbits. One cubic centimeter of broth dilutions of an eighteen hour broth culture of a pleural fluid containing pneumococcus type I was injected into the prepared cavities of these rabbits (seventy-two hours later), with four rabbits used as controls. One cubic centimeter of the dilutions was plated out, and the colonies were counted. (The figures in table 1 and in the two succeeding tables are obtained from the average made from the number of colonies on these plates and represent the approximate number of pairs or chains injected.)

Results.—All the rabbits died except one control and one prepared rabbit which had received the smallest dose (table 1). Apparently there was no protection afforded by this preparation. Animals were not protected against approximately five pairs or chains of pneumococci.

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34. The strain was furnished by Julia T. Parker of the Department of Pathology, College of Physicians and Surgeons, Columbia University.

Three later experiments gave similar results. In one of these, however, slight protection was shown when the broth culture used was made from a pleural fluid which had been kept almost a month, thus possibly being less virulent. Three of the four prepared rabbits survived a small dose which was fatal to the controls. No protection was obtained in two experiments in which gum arabic-broth (instead of aleuronat-starch) was injected into the pleural cavity of the rabbits, which were infected seventy-two hours later with varying doses of eighteen hour broth culture of pneumococcus I.

From these experiments, when a seventy-two hour preparation was used, it can be said that little if any protection is afforded against pneumococcus infection. At the most, animals were protected only against from four to five fatal doses.

As the presence of pleural exudates, with a relatively high number of clasmatocytes and an accumulation of macrophages in thickened

TABLE 1.—*Effect of Seventy-Two Hour Preparation with Aleuronat-Starch on Resistance of Rabbits to Intrapleural Injection of Pneumococcus Type I*

Rabbits	Preparation	Amount of Culture Injected	Results
1561.....	Aleuronat-starch	0.000001 cc. = 50 colonies*	Dead, 26 hours
1574 (control)....	.....	0.000001 cc. = 50 colonies	Dead, 24 hours
5576.....	Aleuronat-starch	0.0000001 cc. = 5 colonies	Dead, 48 hours
1560.....	Aleuronat-starch	0.0000001 cc. = 5 colonies	Dead, 24 hours
5579 (control)....	.....	0.0000001 cc. = 5 colonies	Dead, 48 hours
1576 (control)....	.....	0.0000001 cc. = 5 colonies	Dead, 26 hours
5577.....	Aleuronat-starch	0.00000002 cc. = 1 colony	Survived
5574 (control)....	.....	0.00000002 cc. = 1 colony	Survived

* The number of colonies represents the average number of pairs or chains of organisms injected.

pleural walls, failed to increase the resistance of the rabbits, the question arose whether the presence of a polymorphonuclear exudate and an inflamed pleura with many polymorphonuclears might not protect against pneumococcus. Workers have attributed much importance to the phagocytosis of pneumococcus by these cells. In vitro, the polymorphonuclear as well as the mononuclear cells of these pleural exudates were found to be slightly phagocytic for our strain. Consequently, in two experiments a twenty-four hour preparation of the cavity was used which gives an exudate in which polymorphonuclears predominate. The result of one of these is given in table 2.

Injection of Pneumococcus into Twenty-Four Hour Prepared Pleural Cavity.—EXPERIMENT 2.—Aleuronat and starch were injected into the pleural cavities of six rabbits. Twenty-four hours later, intrapleural injections of 1 cc. of broth dilutions of eighteen hour broth culture of pneumococcus were made into these rabbits and two used as controls.

RESULTS.—All of the rabbits died, even when a dose as small as 0.0000001 cc. of the culture was injected (table 2). Thus apparently no protection was afforded

rabbits against an intrapleural injection of pneumococcus type I when the cavity had been prepared only twenty-four hours previously with aleuronat-starch.

The prepared cavities were not resistant to injections of pneumococcus, neither those containing an exudate predominantly polymorphonuclear with an inflamed pleura nor those containing an exudate with many mononuclear cells and a thickened pleura containing granulation tissue and many macrophages.

The mobilization of clasmatocytes which Gay and his collaborators found produced such a remarkable increase in the resistance of rabbits to intrapleural infections with streptococcus caused no appreciable increase in their resistance to this strain of pneumococcus. There was not much difference in the virulence of these two organisms when they were injected intrapleurally. Less than 0.0000001 cc. of broth cultures of either organism was fatal for rabbits; however, death occurred much more rapidly after an injection of pneumococcus than after one of streptococcus. With the pneumococcus there was rapid invasion of the blood stream from both prepared and normal cavities. This accumulation of cells did not localize the infection. Microscopic examination showed that there was much less phagocytosis of the pneumococcus than of the streptococcus when small

TABLE 2.—*Effect of Twenty-Four Hour Preparation with Aleuronat-Starch on Resistance of Rabbits to Intrapleural Injection of Pneumococcus Type I*

Rabbits	Preparation	Amount of Culture Injected	Results
4551.....	Aleuronat-starch	0.000001 cc. = 100 colonies*	Dead, 24 hours
4567.....	Aleuronat-starch	0.000001 cc. = 100 colonies	Dead, 24 hours
4554.....	Aleuronat-starch	0.0000005 cc. = 50 colonies	Dead, 24 hours
4556.....	Aleuronat-starch	0.0000005 cc. = 50 colonies	Dead, 24 hours
4553 (control)....	.....	0.0000002 cc. = 20 colonies	Dead, 24 hours
4551.....	Aleuronat-starch	0.0000001 cc. = 10 colonies	Dead, 24 hours
4800.....	Aleuronat-starch	0.0000001 cc. = 10 colonies	Dead, 3 days
4530 (control)....	.....	0.0000001 cc. = 10 colonies	Dead, 48 hours

* The number of colonies represents the average number of pairs or chains of organisms injected.

amounts of broth cultures of these organisms were incubated with small amounts of exudates from either twenty-four or seventy-two hour prepared pleural cavities. Seldom did more than from 3 to 5 per cent of the clasmatocytes phagocytose the pneumococcus, while 15 per cent of the clasmatocytes of the same exudates phagocytosed the streptococcus. No pneumococci were found in the macrophages in the few examined walls of the seventy-two hour prepared cavities of rabbits killed shortly after the injection of a relatively large number of organisms.

This lack of protection in prepared cavities might be due to the resistance of our virulent strain of pneumococcus to phagocytosis. Many workers have noted that virulent cultures are not phagocytosed by leukocytes in vitro. Rosenow [35] showed that bacteria which fail to absorb opsonins show great resistance to phagocytosis. With physiologic solution of sodium chloride he was able to extract from virulent pneumococci a substance, "virulin," which inhibited the action of pneumococcus opsonin; after the extraction of the substance from pneumocci, they became phagocytosed. The extracts of virulent pneumococci or the

35. Rosenow, E. C.: J. Infect. Dis. **4**:285, 1907.

filtrates of broth cultures of these organisms possess a soluble substance which reduces the phagocytosis of avirulent pneumococci and increases their virulence (Rosenow,[35] Felton and Bailey [36]).

Injection of Washed Pneumococcus into Seventy-Two Hour Prepared Pleural Cavities.—It was thought possible that these soluble specific substances, "virulins," "aggressins," might be responsible for the failure to get local intrapleural protection against this virulent strain of pneumococcus type I. With this in mind, several experiments were performed to determine whether rabbits offered more resistance to infection with washed organisms than with the unwashed organisms and might be protected against doses of washed pneumococcus by the mobilization of macrophages.

Pneumococci from an eighteen hour broth culture were washed twice in physiologic solution of sodium chloride. Some of the washed organisms were resuspended in broth and others in the Berkefeld filtrate from some of the culture. Corresponding broth dilutions of the suspensions were injected into rabbits having a seventy-two hour prepared cavity and into normal rabbits. In two experiments all of the prepared animals given injections with washed organisms, which had been in contact with the filtrate, as well as all of the control rabbits, died. Only those prepared rabbits survived (two out of three) which had received the smallest doses (from five to thirteen pairs or chains) of the washed organisms resuspended in broth. This showed a slight amount of protection.

The carrying out of well controlled experiments was difficult, as during the process of washing in physiologic solution of sodium chloride and diluting, many of the organisms were either destroyed or so injured that they were sensitive to changes in temperature and to the nature of the medium. Plating showed that some died in the broth in the interval between the making of the dilutions and the infection of the animals. When Locke's solution was used, instead of saline, the decrease in the number of organisms was not so great, and approximately the same number of organisms could be given in corresponding dilutions. Falk and Yang [37] avoided the use of saline for washing pneumococcus on account of a possible detrimental effect. It was found advisable not to subject the organisms to more thorough washing and to use Locke's solution instead of saline.

EXPERIMENT 3.—*A.* Centrifugated organisms from 2 cc. of an eighteen hour broth culture of pneumococcus type I were washed in Locke's solution and then in infusion broth. They were resuspended in broth, and broth dilutions were made. One cubic centimeter of varying dilutions was plated out, and 1 cc. of

36. Felton, L. D., and Bailey, G. H.: J. Infect. Dis. **38**:131, 1926.

37. Falk, I. S., and Yang, S. Y.: J. Infect. Dis. **38**:1, 1926.

these dilutions was injected into the cavities of three rabbits prepared with seventy-two hour aleuronat-starch and into three controls in series A, table 3.

B. Centrifugated organisms from 2 cc. of the eighteen hour broth culture, after being washed in Locke's solution, were washed in the Berkefeld filtrate of a portion of the culture, and resuspended in the filtrate. Broth dilutions were made and 1 cc. of the dilutions was plated and 1 cc. injected into pleural cavities of three prepared and three control rabbits in series B, table 3.

Results.—All the control rabbits of both series died. All the prepared rabbits, receiving the washed organisms, which had been in contact with the filtrate, died. All the prepared rabbits that received the washed organisms, resuspended in broth, died, except the one that received the smallest dose (table 3).

The pneumococci, which had been subjected to several washings in physiologic solution of sodium chloride or in Locke's solution and broth, were still virulent

Table 3.—*Effect of Seventy-Two Hour Preparation with Aleuronat-Starch on Resistance of Rabbits to Intrapleural Injection of Washed Pneumococcus*

A. Pneumococci from broth culture washed in Locke's solution, in broth and resuspended in broth. Dilutions made in broth. Forty-seven colonies from 1 cc. of 1:1,000,000 dilution

Rabbits	Preparation	Amount of Pneumococcus Suspension Injected	Results
1634	Aleuronat-starch	0.000001 cc. = 47 colonies	Dead, 28 hours
1641 (control)	.....	0.000001 cc. = 47 colonies	Dead, 28 hours
1635	Aleuronat-starch	0.0000002 cc. = 10 colonies	Dead, 36 hours
1642 (control)	.....	0.0000002 cc. = 10 colonies	Dead, 36 hours
1636	Aleuronat-starch	0.00000005 cc. = +2 colonies	Survived
1650 (control)	.....	0.00000005 cc. = +2 colonies	Dead, 28 hours

B. Pneumococci from broth culture washed in Locke's solution, in Berkefeld filtrate of portion of culture, and resuspended in filtrate. Dilutions made in broth. Forty-nine colonies from 1 cc. of 1:1,000,000 dilution

Rabbits	Preparation	Amount of Pneumococcus Suspension Injected	Results
1637	Aleuronat-starch	0.000001 cc. = 49 colonies	Dead, 36 hours
1649 (control)	.....	0.000001 cc. = 49 colonies	Dead, 28 hours
1638	Aleuronat-starch	0.0000002 cc. = 10 colonies	Dead, 36 hours
1651 (control)	.....	0.0000002 cc. = 10 colonies	Dead, 24 hours
1639	Aleuronat-starch	0.00000005 cc. = +2 colonies	Dead, 36 hours
1648 (control)	.....	0.00000005 cc. = +2 colonies	Dead, 24 hours

for the rabbits. Animals with prepared cavities were only slightly more resistant to the washed organisms than to the unwashed pneumococci or to those that had been washed and subsequently brought into contact with the broth culture filtrate. There was no marked difference in the susceptibility of the washed and unwashed organisms to phagocytosis in vitro by cells of the exudates, except that with washed organisms the mononuclear cells seemed slightly more active.

These results appear to be in accord with the work of Miss Pittman, which is mentioned by Falk,[38] who considered the specific substances on the pneumococcus, their encapsulation and high potential difference and not the secreted soluble substances important. It would appear from our experiments, in which protection was so slight against the washed

38. Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 565.

organisms, that the soluble specific substance on the pneumococci was not the essential factor in preventing protection by mobilized clasmatocytes in the pleural cavities and adjacent tissues.

As washing the pneumococci made them only slightly more susceptible to phagocytosis by the mononuclear cells of the exudates and the prepared cavity was only slightly more resistant to them, another means of increasing their susceptibility to phagocytosis by the macrophages was sought. It was decided to try antiserum.

ADDITION OF ANTISERUM TO PNEUMOCOCCUS BEFORE INJECTION INTO THE PLEURAL CAVITY

Denys and LeClef [39] noted that the recovery of immunized rabbits from streptococcus infection apparently was due to phagocytosis, made possible by the immune serum. Neufeld and Rimpau,[40] working with serums derived from animals immunized with streptococci and pneumococci, concluded that the serum contained "bacteriotropins" which altered the bacteria so as to make them susceptible to phagocytosis. Kanai [21] injected antiserum with streptococcus into the peritoneum of mice and observed that its protective value was associated with increased phagocytosis by the leukocytes, especially by the mononuclears. Bass,[26] studying bone marrow and intrapleural streptococcus infections in normal rabbits and those that had been immunized intravenously, found increased phagocytosis in the histiocytes and mononuclear cells as well as in the polymorphonuclear cells. Protection against intrapleural streptococcus infection was obtained with immunization and not with twenty-four hour preparation of the cavity alone. There was marked phagocytosis by the histiocytes when he injected sensitized streptococcus into the bone marrow. He concluded that the macrophages react to the opsonized organisms as do the leukocytes, and that immunity depends chiefly on the phagocytosis and digestion of the cocci by the reticuloendothelial system (histiocytes, tissue macrophages or clasmatocytes).

When antiserum diluted with broth was added to our strain of pneumococci, they became susceptible to phagocytosis by the cells of the pleural exudates. After a short incubation, as many as 19 per cent of the polymorphonuclear cells and 34 per cent of the clasmatocytes contained pneumococci. Organisms which had been in contact with antiserum for a short time and had then been resuspended in broth were also susceptible to phagocytosis by the cells. When a sufficient amount of antiserum, e. g., 1 cc., together with our strain of pneumococcus, was injected intrapleurally into a normal rabbit the animal was protected.

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39. Denys, J., and LeClef, J.: Cellule **11**:175, 1895.

40. Neufeld, F., and Rimpau, W.: Deutsche med. Wchnschr. **2**:1458, 1904.

On account of the increase in phagocytosis by the exudate cells of the sensitized pneumococci and the results obtained by Bass [26] with streptococci, it was thought that with the accumulation of clasmatocytes in a prepared pleural cavity, local protection might be obtained against an infection with pneumococci previously in contact with antiserum.

Injection of Pneumococcus that Had Been in Contact with Antiserum in a Seventy-Two Hour Pleural Cavity.—EXPERIMENT 4.—Two cubic centimeters of a broth culture of pneumococcus type I was centrifugated. To the centrifugated organisms was added 0.4 cc. of antipneumococcus serum.[41] After thirty minutes' incubation, 1.6 cc. of broth was added, the organisms were resuspended, and broth dilutions were made. Intrapleural injections of 1 cc. of corresponding dilutions were made into eight normal rabbits and eight rabbits in which the cavities had

TABLE 4.—*Effect of Seventy-Two Hour Preparation with Aleuronat-Starch on Intrapleural Injections of Pneumococcus Type I Which Had Been in Contact with Type I Antiserum*

Rabbits	Preparation	Amount of Suspension Injected	Results
1596.....	Aleuronat-starch	0.0001 cc. = 900 colonies*	Dead, 48 hours
1609 (control)....	.....	0.0001 cc. = 900 colonies	Dead, 24 hours
1597.....	Aleuronat-starch	0.00002 cc. = 180 colonies	Dead, 48 hours
1598.....	Aleuronat-starch	0.00002 cc. = 180 colonies	Dead, 72 hours
1610 (control)....	.....	0.00002 cc. = 180 colonies	Dead, 48 hours
1611 (control)....	.....	0.00002 cc. = 180 colonies	Dead, 48 hours
1599.....	Aleuronat-starch	0.00001 cc. = 90 colonies	Survived
1600.....	Aleuronat-starch	0.00001 cc. = 90 colonies	Survived
1612 (control)....	.....	0.00001 cc. = 90 colonies	Dead, 24 hours
1613 (control)....	.....	0.00001 cc. = 90 colonies	Dead, 48 hours
1601.....	Aleuronat-starch	0.000002 cc. = 18 colonies	Survived
1602.....	Aleuronat-starch	0.000002 cc. = 18 colonies	Survived
1614 (control)....	.....	0.000002 cc. = 18 colonies	Dead, 24 hours
1615 (control)....	.....	0.000002 cc. = 18 colonies	Dead, 24 hours
1603.....	Aleuronat-starch	0.000001 cc. = 9 colonies	Survived
1616 (control)....	.....	0.000001 cc. = 9 colonies	Dead, 48 hours

* The number of colonies represents the average number of clumps of organisms (not pairs or chains) in 1 cc. of broth dilutions. The microscopic examination of broth dilution (1:100) showed organisms mostly in clumps, often containing thirty chains.

been prepared seventy-two hours previously. Broth dilutions were plated out, the colonies were counted and an average was made. The lower dilutions were examined microscopically.

RESULTS.—All the prepared rabbits receiving the three smaller doses of sensitized pneumococcus were protected (table 4). All the control rabbits receiving the same doses died. The prepared rabbits withstood 0.00001 cc. of the suspension of the pneumococci which had been in contact with antiserum, while 0.000001 cc. of the suspension was fatal to the animal used as control.

It was difficult to estimate with any accuracy the number of living organisms injected, as they had been agglutinated by the serum and there were many clumps. The animals were certainly given many more organisms than the figures show. In a preliminary experiment with pneumococci that had been in contact with antiserum, both control rabbit and prepared rabbit lived when 0.0000001 cc. of the

41. The serum used was horse serum, diagnostic pneumococcus type I antiserum from the Department of Health, New York.

suspension was given. When 1 cc. of that dilution was plated out, no colonies were seen, so it is impossible to say whether the unprepared rabbit had received even one clump of organisms. It can at least be said that prepared rabbits (table 4) receiving pneumococci that had been in contact with antiserum were protected against more than ten times the number that was fatal to unprepared animals. The same result had been found in two previous experiments. In a later experiment a rabbit was protected against more than 100 times the fatal dose for an unprepared animal.

These experiments showed that a local protection against pneumococcus I was attained in seventy-two hour prepared pleural cavities containing mononuclear exudates, with thickened pleuras containing many macrophages when the organism had been in contact with a specific immune serum. The protection afforded was almost as marked as that found by Gay and his collaborators against unsensitized streptococcus. These results are somewhat similar to those obtained by Tudoranu,[32] working with type III. He obtained protection in twenty-four hour broth-prepared peritoneums when he injected immune serum previously and simultaneously with the organisms, but not when he injected normal serum. He noted that phagocytosis was negligible unless immune serum had been injected. He considered that the antibodies, neutralizing the aggressins, permitted the production of an exudate, rich in leukocytes, which changes the pneumococci and renders them susceptible to phagocytosis.

Gay and his collaborators, in their local passive immunity experiments (Gay and Morrison,[22] Gay and Clark[23]), found a more rapid disappearance of streptococci from the pleural cavity when rabbit immune serum was given both previously and simultaneously with the injection than when normal serum was used. Streptococci showed greater susceptibility to phagocytosis by the exudate cells with immune serum than with normal serum. In the experiments with pneumococci the effect of the addition of normal rabbit or horse serum was not tried, but it is indicated by the result obtained in a later experiment designed to give some suggestions regarding the mechanism of this protection. It appears that in order to get local protection against this virulent strain of pneumococcus type I by the seventy-two hour preparation of the cavity, the organisms must first be altered by contact with immune serum and become susceptible to phagocytosis.

If the addition of a serum with its specific immune properties (demonstrable antibodies such as agglutinins and bacteriotropins) to the pneumococcus was necessary in order to obtain protection in prepared pleural cavities of rabbits, the reduction of the antibodies in the serum should lessen the protective value of the serum and thus decrease the resistance afforded by the accumulation of the macrophages.

Gay and Chickering,[42] with the addition of an extract of pneumococcus to homologous antiserum, produced a precipitate which carried down the antibodies that protect animals against pneumococcus infection. Felton and Bailey [43] extracted a specific substance from pneumococcus type II, which was nontoxic for mice but gave an antagonistic effect on the defense of these animals or increased the virulence of the organisms. They observed that it neutralized the protective effect of the pneumococcus serum in vivo and in vitro. With this soluble specific substance all protective substances could be precipitated. The agglutinative, precipitative and tropinizing activities were absorbed out of the serum by the filtrate. Wadsworth and Sickles [44] found that the supernatant fluid or filtrate of broth culture of a virulent strain of type I had an inhibitory effect on phagocytosis of virulent strains in the presence of specific antiserum, and that this action was on the serum rather than on the leukocytes.

The effect of the addition of a filtrate from a fourteen day broth culture of our strain of pneumococcus to the antiserum was observed in vitro. When the Berkefeld filtrate of a fourteen day broth culture of this strain was added to some of the antiserum a precipitate was formed. Centrifugated organisms from an eighteen hour culture when resuspended in the resulting supernatant fluid were not so completely agglutinated nor so readily phagocytosed by the exudate cells as the organisms that had been resuspended in the antiserum in broth. When small amounts of these two suspensions were incubated with a pleural exudate, those in the antiserum in broth were found in 19 per cent of the polymorphonuclear and 34 per cent of the mononuclear cells, whereas those suspended in the supernatant fluid were phagocytosed only by 7 per cent of the polymorphonuclear and 16 per cent of the mononuclear cells.

The addition, then, of a Berkefeld filtrate of the fourteen day broth culture to the antiserum removed some of its agglutinative and tropinizing activities.

Rabbits were given intrapleural injections of pneumococci which had been in contact with the resulting supernatant fluid in order to determine whether protection could be obtained.

Injection of Pneumococci Which Had Been in Contact with Antiserum After the Addition of Filtrate of a Broth Culture.—EXPERIMENT 5.—*A.* Infusion broth, 1.6 cc., was added to 0.4 cc. of antiserum and this mixture was added to the centrifugated organisms from 2 cc. of an eighteen hour broth culture of pneumo-

42. Gay, F. P., and Chickering, H. T.: J. Exper. Med. **21**:389, 1915.

43. Felton, L. D., and Bailey, G. H.: J. Infect. Dis. **38**:145, 1926; (footnote 36).

44. Wadsworth, A. B., and Sickles, G. M.: J. Immunol. **14**:321, 1927. Sickles, G. M.: Ibid. **14**:329, 1927.

coccus. After thirty minutes broth dilutions of the suspension were made, and 1 cc. of dilutions was plated out; intrapleural injections of 1 cc. were made into rabbits in series A, table 5. Four rabbits had received aleuronat-starch intrapleurally seventy-two hours previously, and three normal rabbits were used as controls.

B. Two cubic centimeters of a Berkefeld filtrate of a fourteen day culture of the pneumococcus was added to 0.5 cc. of antiserum. This mixture was centrifugated after standing one hour, and 2 cc. of the supernatant fluid was added to the centrifugated organisms from 2 cc. of the eighteen hour broth culture of pneumococcus. Half an hour later, dilutions of this suspension were made in broth. Broth dilutions were plated out in 1 cc. amounts and injections of 1 cc. were made into the pleural cavities of the rabbits in series B, table 5. Four

TABLE 5.—*Effect of the Addition of Broth Culture Filtrate to Antiserum on Resistance of Rabbits to Intrapleural Injections of Pneumococcus, After Seventy-Two Hour Preparation with Aleuronat-Starch* *

A. Injection of broth dilutions of suspension of pneumococcus which had been in a mixture of antiserum and broth

Rabbits	Preparation	Amount of Suspension Injected		Results
1623	Aleuronat-starch	0.00002 cc.	= 1,600 colonies	Survived
1621	Aleuronat-starch	0.00001 cc.	= 800 colonies	Survived
1625	Aleuronat-starch	0.000002 cc.	= 160 colonies	Survived
1632 (control)	.....	0.000002 cc.	= 160 colonies	Dead, 72 hours
1630	Aleuronat-starch	0.000001 cc.	= 80 colonies	Survived
1645 (control)	.....	0.000001 cc.	= 80 colonies	Dead, 24 hours
1640 (control)	.....	0.0000002 cc.	= 16 colonies	Dead, 48 hours

B. Injection of broth dilutions of suspension of pneumococcus which had been in supernatant fluid from the mixture of antiserum and Berkefeld filtrate of fourteen day broth culture

Rabbits	Preparation	Amount of Suspension Injected		Results
1626	Aleuronat-starch	0.00001 cc.	= 2,000 colonies	Dead, 24 hours
1627	Aleuronat-starch	0.000002 cc.	= 400 colonies	Dead, 24 hours
1633 (control)	.....	0.000002 cc.	= 400 colonies	Dead, 48 hours
1631	Aleuronat-starch	0.000001 cc.	= 200 colonies	Dead, 36 hours
1643 (control)	.....	0.000001 cc.	= 200 colonies	Dead, 24 hours
1622	Aleuronat-starch	0.0000002 cc.	= 40 colonies	Dead, 24 hours
1644 (control)	.....	0.0000002 cc.	= 40 colonies	Dead, 24 hours

* The number of colonies represents the clumps of organisms, not the pairs or chains. Microscopic examination of the broth dilution (1:10) of organisms used in series A showed organisms mostly in clumps with an average of thirty-four chains; 1:10 dilution of those used in B showed fewer and smaller clumps, with an average of eight chains.

rabbits had received intrapleural injections of aleuronat-starch seventy-two hours previously, and three normal rabbits were used as controls.

RESULTS.—All of the prepared rabbits survived in series A (table 5); all of the control rabbits died. All the animals, both prepared and controls, died in series B (table 5).

All the prepared animals were protected against the organisms that had been in contact with antiserum and broth. A rabbit was protected against approximately 1,600 clumps of pneumococci, which was 100 times the number that was fatal to a control rabbit (rabbits 1623, 1640, table 5). None of the rabbits was protected against the pneumococci that had been in the supernatant fluid from the antiserum and culture filtrate; a prepared rabbit did not withstand a dose containing approximately forty clumps of these pneumococci (rabbit 1622, table 5).

This experiment shows that by the addition of culture filtrate to the antiserum, which decreases its agglutinating and tropinizing effect, there had been a decrease in the protective value. It indicates that contact of the pneumococcus with a

serum containing these properties is necessary before protection can be obtained in a rabbit by a preparation that causes an accumulation of macrophages.

The failure to obtain protection against our strain of pneumococci by a seventy-two hour preparation, which causes an accumulation of macrophages in the pleural cavity and affords a marked protection against sensitized pneumococci, would appear to be due to an insufficient amount of agglutinative and tropinizing activity in the rabbit.

Robertson and Sia [45] found that the serum of resistant animals, dogs and cats, possessed pneumococcidal properties, but that that of susceptible animals, as rabbits, did not. Virulent pneumococci, after contact with serum of resistant animals, were phagocytosed by the leukocytes from susceptible as well as from resistant animals, but this was not the case after contact with serum of susceptible animals. They considered opsonins important in resistance to pneumococcus infections. Bull [46] considered agglutinins, as well as opsonins, important.

Injection of Pneumococci That Had Been in Contact with Antiserum into an Eighteen Hour Prepared Cavity.—As the seventy-two hour preparation of the pleural cavity afforded protection against pneumococcus that had been in contact with antiserum, the question arose as to whether it was necessary to have an accumulation of macrophages for protection or whether an accumulation of polymorphonuclear cells would protect the rabbits against these organisms. The polymorphonuclear cells of the pleural exudate in vitro had appeared also phagocytic for the pneumococcus that had been in contact with the antiserum. In eighteen hours an injection of aleuronat-starch produces an exudate rich in polymorphonuclear cells. Table 6 gives the results of the infection of an eighteen hour prepared cavity with pneumococci that had been in contact with antiserum.

EXPERIMENT 6.—Two cubic centimeters of a twenty hour broth culture of the pneumococcus was centrifugated. To these organisms 0.4 cc. of antiserum was added. After thirty minutes, 1.6 cc. of broth was added, and the suspension was diluted in broth. Intrapleural injections of 1 cc. of some of the broth dilutions were made into two normal rabbits and three rabbits that had received injections of aleuronat-starch eighteen hours previously.

RESULTS.—As table 6 shows, no protection was apparent. A prepared rabbit receiving only 0.000001 cc. of the suspension (eight clumps) was not protected (rabbit 1579, table 6).

The same results were shown in a later experiment. An inflamed pleural cavity containing an exudate predominantly polymorphonuclear does not protect rabbits against the injection of pneumococci that have been in contact with antiserum.

45. Robertson, O. H., and Sia, R. H.: J. Exper. Med. **39**:219, 1924; ibid. **46**:237, 1927.

46. Bull, C. G.: J. Exper. Med. **22**:457, 1915; ibid. **24**:7, 1916.

As the rabbits with seventy-two hour prepared cavities are protected against more than 100 times the number of treated pneumococci which are still fatal for unprepared rabbits or for those with eighteen hour prepared cavities, it would appear that the protection is essentially due to the accumulation of clasmatocytes.

A few studies were made of the action of a seventy-two hour pleural exudate on the pneumococcus in vitro and in vivo to determine whether the exudate played an important part in the protection.

The Injection of Seventy-Two Hour Pleural Exudate and Pneumococci that Had Been in Contact with Antiserum into the Normal Pleural Cavity.—EXPERIMENT 7.—The centrifugated organisms from 2 cc. of a twenty hour broth culture

TABLE 6.—*Effect of Eighteen Hour Preparation with Aleuronat-Starch on Intrapleural Injections of Pneumococcus Type 1 Which Had Been in Contact with Antiserum*

Rabbits	Preparation	Amount of Suspension Injected	Results
1570.....	Aleuronat-starch	0.00001 cc. = 80 colonies*	Dead, 48 hours
1579.....	Aleuronat-starch	0.000001 cc. = 8 colonies	Dead, 28 hours
1572 (control)....	.....	.....	Dead, 28 hours
1568.....	Aleuronat-starch	0.0000001 cc. = ?	Lived
1572 (control)....	.....	.....	Lived

* The number of colonies represents the average number of clumps of organisms in 1 cc. of broth dilutions of suspension of sensitized pneumococcus injected.

TABLE 7.—*Effect of Intrapleural Simultaneous Injection of Seventy-Two Hour Gum Arabic-Broth Pleural Exudate with Pneumococcus Which Had Been in Contact with Antiserum*

Rabbits	Injection	Amount of Suspension Injected	Results
1619.....	2 cc. exudate	+0.00001 cc. = 90 colonies*	Dead, 50 hours
1621 (control)....	Broth	+0.00001 cc. = 90 colonies	Dead, 36 hours
1620.....	2 cc. exudate	+0.000001 cc. = 9 colonies	Dead, 36 hours
1628 (control)....	Broth	+0.000001 cc. = 9 colonies	Survived

* The number of colonies represents the average number of clumps of organisms in 0.5 cc. of dilutions of suspension of pneumococcus injected.

of pneumococcus were in contact with antiserum for twenty minutes. They were resuspended in broth, and broth dilutions were made. Then 0.5 cc. of the dilutions was added to 2 cc. of seventy-two hour pleural exudate and injected intrapleurally into normal unprepared rabbits. Injections of 0.5 cc. of corresponding dilutions of the organisms without the exudate were made into two other rabbits.

RESULTS.—Both rabbits receiving the exudate and the organisms died. The exudate did not protect a rabbit against an intrapleural dose not fatal to one that had received no exudate (table 7, 1620, 1628).

The transfer of a seventy-two hour pleural exudate to the normal pleural cavity does not protect rabbits against the pneumococci that had been in contact with antiserum. This experiment would suggest that the exudate does not have a bactericidal effect in vivo on the pneumococcus, nor does it play an important rôle in the local protection obtained against the pneumococcus by the seventy-two hour preparation of the pleural cavities of the rabbits.

In spite of the fact that the exudate did not confer protection on normal cavities against pneumococci that had been in contact with immune serum, it was thought there might be some bactericidal or inhibitory action by the exudate.

ACTION IN VITRO OF PLEURAL EXUDATE ON PNEUMOCOCCUS

In several experiments the pleural exudates had shown no bactericidal effect in vitro on our virulent strain of pneumococcus. The supernatant fluid from the exudate showed no bactericidal effect on these organisms, and they were not susceptible to phagocytosis by the cells. The contact with antiserum rendered them more susceptible to phagocytosis. Woo [47] found that a rabbit serum-leukocyte mixture had the power to kill avirulent pneumococcus but did not inhibit the growth of virulent organisms.

Tests were made to determine whether the exudate might have a bactericidal effect on the organisms that were washed or had been washed and in contact with antiserum.

TABLE 8.—*Bactericidal Effect of Exudate on Organisms*

	Results, 24 Hours
1. Exudate 1 cc. + 0.1 cc. pneumococcus (±150)	Growth
2. Exudate 1 cc. + 0.1 cc. pneumococcus which had been washed in Locke's solution and broth (±47)	Growth
3. Exudate 1 cc. + 0.1 cc. pneumococcus which had been washed in Locke's solution and broth and in contact with antiserum (±34)	Growth

Bactericidal Effect of Exudate in Vitro.—EXPERIMENT 8.—Portions of a broth culture of pneumococcus were centrifugated and washed in Locke's solution. The sediment in one tube was washed in broth and resuspended in broth; the sediment in the second tube was placed in contact with antiserum and then resuspended in broth. Broth dilutions were made of the broth culture and of these suspensions. One-tenth of a cubic centimeter of dilution 1:100,000 of each of these was added to 1 cc. amounts of a seventy-two hour pleural exudate. (These were incubated at 37 C., and tested for sterility on blood-agar plates twenty-four hours later.) The number of chains or clumps of pneumococcus are indicated by the figures in table 8.

RESULT.—Growth was evident in the subcultures made from all of the tubes after twenty-four hours. In twenty-four hours the exudate had not been able to kill the small number of washed pneumococci and those that had been in contact with antiserum. The exudate showed no apparent bactericidal action on the pneumococcus.

In other experiments growth was obtained in the subcultures when as few as eight clumps of organisms that had been in contact with antiserum were added to the exudate and incubated for eighteen hours. On the other hand, Robertson and Sia [48] were not able to recover pneumo-

47. Woo, S. T.: J. Exper. Med. **43**:623, 1926.

48. Robertson, O. H., and Sia, R. H.: J. Exper. Med. **40**:467, 1924.

coccus after immune serum was added to a rabbit serum-leukocyte mixture. They used a mechanical agitator, and a larger amount of immune serum was present in their mixture than was still present in the broth dilution used by my co-workers and myself.

It was thought that microscopic examination might show slight evidence of growth inhibition as well as of marked phagocytosis by the exudate of the pneumococci to which antiserum had been added. Observations were made of the action in vitro of seventy-two hour

TABLE 9.—*Microscopic Observation of Phagocytosis and Growth of Pneumococcus in Seventy-Two Hour Pleural Exudate in Vitro*

Tube 1: Exudate plus Broth Dilution of Pneumococci Which Had Been in Contact with Antiserum and Broth

Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½	8	10	4 (mostly clumps)
1	5	13	6 (mostly clumps)
2	2	7	5 (mostly clumps)

Tube 2: Exudate plus Broth Dilution of Pneumococci Which Had Been in Contact with Supernatant Fluid of Mixture of Antiserum and Filtrate

Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½	1	5	70 (some small clumps)
1	2	7	80 (some small clumps)
2	0	5	300 (pairs and chains)

Tube 3: Exudate plus Broth Dilution of Pneumococci Which Had Been Resuspended in Broth

Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½	0	2	98 (pairs and chains)
1	2	0	160 (pairs and chains)
2	0	0	300 (pairs and chains)

Tube 4: Exudate plus Broth Dilution of Pneumococcus Broth Culture

Interval, Hours	Phagocytic Polymorphonuclears, per Cent	Phagocytic Mononuclears, per Cent	Extracellular Bacteria (100 Cells Counted)
½	0	2	45 (pairs and chains)
1	0	0	100 (pairs and chains)
2	0	0	140 (pairs and chains)

pleural exudates on organisms that had been in contact with antiserum. At the same time the observations included the effect of the addition of fourteen day broth culture filtrate to the antiserum. Broth dilutions of the culture and the broth suspension of the centrifugated organisms from some of the culture were used as controls.

EXPERIMENT 9.—To the centrifugated pneumococcus from 2 cc. of broth culture 0.4 cc. of antiserum plus 1.6 cc. of broth were added and incubated for twenty minutes. The supernatant fluid from a mixture of 0.4 cc. of antiserum and 1.6 cc. of filtrate of fourteen day broth culture was added to the centrifugated organisms from 2 cc. of the culture and incubated for twenty minutes. The centrifugated organisms from 2 cc. of the culture were resuspended in broth. Dilutions were

made in broth of suspensions and of the broth culture. One tenth of a cubic centimeter of the 1:10 dilutions was added to 0.1 cc. of seventy-two hour gum arabic pleural exudate and incubated for two hours. Stained smears were examined at different intervals.

Results.—The pneumococci that had been in contact with antiserum were phagocytosed by the cells of the pleural exudate. The organisms did not appear to have multiplied within two hours. Those that had been in contact with the antiserum to which the filtrate had been added were not so susceptible to phagocytosis, and they had multiplied during the two hours. Very few of the untreated organisms from the culture were phagocytosed, and they were able to multiply in the exudate. Those organisms that had been in contact with antiserum showed

Table 10.—*Study of Pleural Exudates from a Series of Rabbits Prepared by Injection of Aleuronat-Starch Followed from Sixty-Eight to Seventy-Two Hours Later by Injection of Relatively Large Dose of Pneumococcus Type I; 1 Cc. of Culture or Suspensions Injected*

A. Injection of 1 Cc. of Suspension of Pneumococcus Which Had Been in Contact with Antiserum and Broth

Rabbit	Dose*	Interval After Injection	Amount of Fluid, Cc.	Number of Cells in Millions per Cc.		Ratio of Bacteria Recovered to Those Injected	Percentage of Phagocytic Cells		Extracellular Bacteria, 100 Cells Counted	Presence of Pneumococcus in Blood	Presence of Pneumococcus in Left Cavity
				Polymorphonuclears	Mononuclears		Polymorphonuclears	Mononuclears			
1435	2,000,000	45 min.	6.5	47	8	0†	1	7	2	0	0
4598	10,000,000	1 hr.	5	?	?	×0.0001	—	—	0	0	0
608	5,000,000	2½ hr.	3	94	30	×0.0006	0	3	1 (200 cells counted)	0	0

B. Injection of 1 Cc. of Broth Suspension of Centrifugalized Pneumococcus from Broth Culture

1534	9,000,000	45 min.	2.5	60	9	× 8	0.2	4	92	+	+
4597	45,000,000	1 hr.	6	?	?	× 0.26	1	1	38	+	0
690‡	200,000,000	2½ hr.	7	121	34	× 4.3	0.5	0	410	+	+

* Figures under dose in series A represent the number of clumps; in series B, the number of pairs or chains of pneumococci.
† No colonies were seen when 0.5 cc. of exudate was plated out.
‡ 1 cc. of broth culture in 690.

susceptibility to phagocytosis by the exudate cells and to an inhibiting action of the exudate.

Fate of Pneumococcus in the Seventy-Two Hour Prepared Pleural Cavity.—A study was made of the fate of pneumococcus injected into the pleural cavities of a few rabbits prepared seventy-two hours previously with aleuronat-starch in order to obtain information that would explain still further the mechanism of the protection.

Injections of 1 cc. of broth cultures of the pneumococcus or broth suspensions of centrifugated organisms from broth cultures and organisms that had been in contact with antiserum and resuspended in broth were made. The animals were killed at different intervals. The exudates were removed and portions plated out to determine the presence and number of viable organisms. The exudates were examined microscopically for phagocytosed and extracellular bacteria. Cultures

were made from the other pleural cavity and from the heart's blood. Table 10 gives the results of the observations.

RESULTS.—Very few organisms were recovered from the pleural exudates of the rabbits into which injections of organisms that had been in contact with antiserum were made. There was a marked decrease in the number of viable organisms shown in the time intervals up to two and one-half hours. Microscopically, it was difficult to observe organisms in the exudate from these rabbits. On the other hand, with one exception there had been an increase in the number of organisms in the pleural cavities of the rabbits given injections with the organisms that had not been in contact with antiserum. There was only a small amount of phagocytosis. These organisms were found in the heart's blood in as short a time as forty-five minutes after injection; in two animals they were recovered from the uninoculated pleural cavity, whereas in the rabbits into which injections of sensitized pneumococci were made no organisms were recovered within two and one-half hours from the heart's blood or from the other pleural cavity.

The virulent pneumococci, not altered by immune serum so that they were not clumped or susceptible to phagocytosis, were capable of multiplying in the exudate in the prepared pleural cavity and rapidly invading the blood stream. These observations made for the few time intervals up to two and one-half hours suggest that the growth of the sensitized pneumococcus had been retarded and the spread of the organisms checked in a pleural cavity with an exudate containing many mononuclear as well as polymorphonuclear cells and a thickened pleura containing granulation tissue and many macrophages.

The rapid disappearance of these sensitized organisms from the exudate may be due to their phagocytosis by the mobilized cells in the thickened pleura of these seventy-two hour prepared pleural cavities. The thickened pleura containing many cells may prevent clumped or phagocyted organisms from entering the blood stream.

To increase the resistance of rabbits and obtain local protection in the pleural cavity against virulent pneumococcus several factors are involved. In addition to a prepared cavity, with the accumulation of clasmatocytes and a thickened wall, the contact of the organisms with immune serum is necessary. The pneumococci then become clumped and susceptible to phagocytosis by the polymorphonuclear and mononuclear cells of the exudate, and their growth is retarded. These organisms —many clumped, others within the polymorphonuclear and mononuclear cells and a few free pairs or chains susceptible to phagocytosis by the clasmatocytes—may be confined in the pleural cavity by the thickened wall with its granulation tissue and many macrophages, and the rabbit may be protected.

In immunized rabbits, Singer and Adler obtained protection in prepared and unprepared cavities against pneumococcus type III. They attributed the protection to a change in the reticulo-endothelial cells and not to the circulating antibodies. Tudoranu emphasized the importance of antibodies in the protection against pneumococcus type III in prepared cavities of passively immunized rabbits. He considered that the antibodies neutralizing the aggressins accelerate the production of the exudate active against the pneumococci.

In our work we have gone a step further than these observers, since we prove conclusively that the accumulation of clasmatocytes, and in addition the action of tropinizing antiserum is necessary to protect a sensitive area of the rabbit against a virulent pneumococcus.

SUMMARY AND CONCLUSIONS

This paper attempts to show what effect the accumulation of polymorphonuclears or of mononuclears in local areas may have on protection against pneumococcus infections.

The strain of pneumococcus type I used was found virulent for rabbits, producing an extensive pleurisy and a rapid invasion of the blood stream. This strain of pneumococcus washed in saline or sensitized by contact with antiserum was still virulent.

Mobilization of the cells was effected by the injection of aleuronat-starch. An eighteen hour preparation of the pleural cavity produces an exudate predominantly polymorphonuclear in character and an inflamed wall filled with polymorphonuclear cells. A seventy-two hour preparation produces an exudate predominantly mononuclear and a thickened wall filled with granulation tissue and many macrophages.

No protection was afforded rabbits against an intrapleural infection with pneumococcus type I by an eighteen hour previous preparation of the pleural cavity.

Slight, if any, protection was afforded rabbits against an intrapleural infection with pneumococcus type I, washed or unwashed, by a seventy-two hour preparation.

Neither normal nor eighteen hour prepared cavities, with polymorphonuclear exudates and an inflamed pleural wall, afforded protection against pneumococci that had been in contact with small amounts of antiserum.

A seventy-two hour preparation afforded a marked protection against pneumococci that had been in contact with the same amount of immune serum. A pleural cavity with an exudate rich in mononuclear cells and a thickened wall with granulation tissue and many macrophages protected the rabbit against a dose of sensitized pneumococci which was from ten to 100 times that which was fatal for normal rabbits or rabbits with acutely inflamed cavities.

From this study it appears that there is a definite correlation between accumulation of clasmatocytes and resistance to pneumococcus infection in the pleural cavity of the rabbit. To obtain complete protection in rabbits against local infections with pneumococcus type I, however, the addition of serum antibodies is necessary.

Laboratory Methods and Technical Notes

ESTIMATION OF HEMOGLOBIN BY CELL CONCENTRATION

Suggestions for Reclassification of the Anemias *

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The present methods of estimating the hemoglobin content colorimetrically are subject to certain errors. Aside from technical difficulties, for example, those of the comparison of colors, the chief source of error appears to be the differences in the relative concentration of the erythrocytes. This may be easily shown in any one case by the determination of the cell-plasma ratio [1] at various times during the day. The proportion of cells to plasma undergoes physiologic variation owing chiefly to the inhibition of fluids, and to exercise and sweating.

With this in mind, I found that under ideal conditions governing the particular technical procedure estimations of the hemoglobin content in the same case not infrequently varied 10 per cent on the same day. This was always due to a change in the relative dilution of the erythrocytes by blood plasma. In order to determine the extent of this variation, the hemoblobin content of several hundred patients was studied both by the old and by the new methods. The latter consisted, in principle, of a complete centrifugation of the cellular elements and determination of the hemoglobin content undiluted by plasma.

METHOD

1. Shake a few grains of dry, powdered sodium citrate into a clean, dry capillary glass tube having an inside diameter of 4 mm. and a length of 10 cm.[2]

2. Holding the tube in the horizontal position or with the distal end slightly depressed, apply the proximal end to a bleeding puncture wound. A rapid, deep, incised wound of the finger made with a sharp lancet-headed needle will fill at least three such tubes with little or no pressure on the finger.

3. Fill the tube about two-thirds full and mix the blood with the citrate by alternately elevating and depressing one end.

4. Allow the blood to gravitate to one end, seal that end with a plug of paraffin and place a broad rubber band snugly around the length of the tube, thus sealing both ends. It is well to file the cut edges to avoid injury to the fingers or tearing of the rubber band.

5. Centrifugate at high speed (plugged end down) for a sufficient length of time to secure the maximal separation of cells and plasma. This is determined as the period of time after which repeated centrifugation no longer diminishes the

* Submitted for publication, April 26, 1929.

* From the Laboratory of St. Bartholomew's Hospital.

1. Felsen, J.: The Cell-Plasma Ratio, Arch. Path. **8**:269 (Aug.) 1929.

2. Felsen, J.: A Simple Method of Testing for Blood Compatibility, Arch. Path. **4**:552 (Oct.) 1927.

length of the cell column. Once established, the same button on the rheostat and the same period of time may be used with every specimen.

6. File-mark the capillary tube (*a*) at the junction of the paraffin plug with the cell column and (*b*) at the junction of the cell column with the plasma column. Break off at both points, thus isolating the cells.

7. By means of a Sahli pipet, graduated at 10 and 20 mm., the tip of which is applied directly to either of the open ends of the cell column, draw up the cells to the mark "10" (10 c.mm.). Add this to the graduated Sahli tube containing tenth normal hydrochloric acid to the mark 10. Wash the pipet thoroughly by sucking up and expelling some of the same fluid. Shake the mixture well and then allow it to stand at least one minute or until the maximal change of color has been effected. Dilute with water to match the standard. When the Dare instrument is used, aspirate the cells from the capillary tube by means of a Sahli pipet, as before, to the mark "10." Then continue aspirating physiologic sodium

A Comparison of the Old and the New Methods of Estimating the Percentage of Hemoglobin in the Blood

Patient	Hemoglobin, per Cent		Red Cell Count	Cell-Plasma Ratio
	Old Method	New Method		
1	55	60	.....	0.66
2	80	75	4,670,000	0.50
3	95	90	5,010,000	0.99
4	85	95	4,390,000	0.63
5	80	82	4,170,000	0.72
6	90	74	4,480,000	....
7	98	80	5,250,000	....
8	90	90	4,680,000	0.66
9	84	75	5,120,000	0.80
10	90	80	4,860,000	0.60
11	75	85	4,280,000	0.56
12	55	60	.....	0.66
13	60	65	.....	1.10
14	70	75	3,580,000	0.28
15	75	70	4,280,000	0.56
16	90	94	4,480,000	0.75
17	110	80	7,040,000	1.50
18	50	65	3,000,000	0.22
19	70	70	3,340,000	0.50
20	80	82	.....	0.72

chloride solution to the mark "20." Eject the resulting mixture (10 c.mm. of cells and 10 c.mm. of saline solution) on to a hanging drop slide or a small watch glass. Mix thoroughly by alternately aspirating and expelling the mixture from the pipet, four or five times. Having secured a uniform mixture, take it up in the Sahli pipet and fill the Dare automatic pipet; the 20 c.mm. of fluid will completely fill the latter. Compare in the colorimeter.

This method of estimating hemoglobin on the basis of the concentration of the capillary cells has been in use in this laboratory for three years and has given uniformly accurate results in conjunction with the Sahli standard. It appears to possess a distinct advantage in that the estimations are made directly on undiluted cells. The factor of plasma dilution, which is well beyond the control of the examiner, is eliminated, regardless of the time of day.

The table records cases chosen from a series of several hundred in which the hemoglobin was estimated on the Sahli and Dare instruments by the old method and by the method based on concentration of the cells. The Sahli figures alone are given. In a comparison of similar

figures in the records of routine examinations made over a period of three years, the following conclusions were reached:

When the cell-plasma ratio $\frac{c}{p}$ approximates 1 (i.e., when the cell column and the plasma column are approximately equal), the estimation of the percentage of hemoglobin by the cell concentration method yields a value most nearly approaching that obtained by the old method.

When the cell-plasma ratio is low (i.e., when the plasma content of the blood is relatively high), the new method gives a considerably higher percentage of hemoglobin than the old (patient 18). This is least marked when the red cells are impoverished in hemoglobin while the red cell count is high (patients 14 and 19).

In primary anemias, the cell-plasma ratio being low, the percentage of hemoglobin is found to be much higher than with the old method.

In chlorosis, the cell-plasma ratio being high, the percentage of hemoglobin is found to be the same or lower than with the old method, by reason of the low hemoglobin content of individual cells.

In polycythemia vera, the cell-plasma ratio being high, the percentage of hemoglobin is found to be lower than with the old method.

In secondary anemias associated with acute hemorrhage, the cell-plasma ratio being low, the percentage of hemoglobin is found to be either normal or low. This is due to the fact that cells are lost, rather than hemoglobin, the percentage of the latter being frequently normal as estimated by the concentration method. The difference between the old method and the new is due to the fact that the latter eliminates one variable factor—the diluent plasma. The importance of this observation is evident in repeated examinations of a patient with bleeding gastric or duodenal ulcer. Watching the cell-plasma ratio will be found a much more reliable index than estimation of the percentage of hemoglobin and the number of erythrocytes.

In secondary anemias associated with dehydration (cachexia, inanition), the cell-plasma ratio being high, the percentage of hemoglobin will be found lower by the new method because the cells have already been concentrated in vivo.

These observations suggest a new concept of anemias. Anemias may be divided into:

1. Cytanemia: This classification embraces the majority of the types of anemias and is due to a diminution in the number of the red blood cells. It includes secondary and primary (pernicious) anemias. The number of erythrocytes is low, the percentage of hemoglobin is normal or almost so, the color index tends to be high, and the cell-plasma ratio is low (less than 1).

2. Hemoglobinemia: This classification includes some secondary anemias and chlorosis. Here the percentage of hemoglobin is low, the number of erythrocytes is normal or increased, the color index is 1 or less and the cell-plasma ratio is 1.

It is interesting to note that in polycythemia vera the percentage of hemoglobin is normal, the number of erythrocytes is greatly increased, the color index is 1 or less and the cell-plasma ratio is high (more than 1).

Some secondary anemias and aplastic anemia fall in an intermediate group between 1 and 2. The foregoing simple classification of anemies

is based on the determination of whether the cells or the hemoglobin are primarily involved. The use of the cell-plasma ratio and the estimation of the hemoglobin content by the cell concentration method appear to be satisfactorily adapted for such a procedure.

A SIMPLE METHOD FOR THE ISOLATION OF ANAEROBIC BACTERIA*

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In this paper I report a simple method of isolation of pure cultures of anaerobic bacteria from blood and other materials from patients.

For the culture of blood, 2 cc. of the citrated specimen is added to a tube containing about 15 cc. of melted agar, and the mixture poured into a Petri dish. After inoculation, the plate is chilled in the icebox until the agar is firm; sterile melted petrolatum is then poured over the surface of the plate to give a layer about 1 cm. in depth. For the culture of surgical swabs, pus and other material, the same procedure is used with the exception that plates are prepared with several different dilutions of the test material to insure obtaining discrete colonies.

The plates are incubated in the usual way.

No difficulty is experienced in the detection of colonies on positive cultures. When it is desired to pick the colonies for transplanting or for staining, the plate is chilled and the hardened layer of petrolatum is easily lifted away with a sterile wooden tongue depressor. If the plate contains gas-formers, it is best to make transplants before the production of gas causes disruption of the culture medium and bubbling of the petrolatum layer.

The simplicity of the method makes possible the inclusion of an anaerobic agar plate as a routine procedure in the culture of all material sent for test to the bacteriologic laboratory of the hospital. It is highly desirable that anaerobic plate cultures should always be included, but the usual methods have required special apparatus or time-consuming procedures that make too great a demand on the resources of the usual hospital laboratory. The method described is as simple as the aerobic plate culture, and at the same time is an effective means of isolating pure cultures of anaerobic bacteria from the infectious material examined in clinical laboratories. During the past three years in the Vanderbilt University Hospital, the anaerobic plates made by this method have frequently shown the presence of anaerobic streptococci and anaerobic bacilli when the aerobic flask cultures and the aerobic plate cultures of the same blood or the same pus have been negative.

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* Submitted for publication, May 16, 1929.

* From the Hospital of the Vanderbilt University Medical School.

General Review

THE RETICULO-ENDOTHELIAL SYSTEM IN PROTOZOAN INFECTIONS *

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The reticulo-endothelial system in relation to the pathogenic protozoa has been the subject of numerous reports. The amount of work on this subject has increased in recent years, particularly as various authors have attempted to analyze more closely the mode of reaction between the body and the infectious organism. The present review has attempted to collect and summarize this work with particular attention to the host's cellular reactions rather than to the activities of the parasite.

Only brief notice can be taken here of the history of the reticulo-endothelial conception and of the morphology of the reticulo-endothelial system. Full accounts of these important points may be found in the reviews to be mentioned.

HISTORY OF THE RETICULO-ENDOTHELIAL CONCEPTION

Metchnikoff [1] recognized the widespread occurrence throughout the body of a group of closely related cells possessing great phagocytic powers. He designated this group the macrophage system. He included in it not only the reticulum cells of the splenic pulp and the lymph nodes, certain endothelial cells, the Kupffer cells and the large mononuclears of the blood and the lymph, but also the nerve cells, on account of their phagocytosis of lepra bacilli, and the neuroglia cells. The criterion that he used in marking out his macrophage system was the phagocytic power of the cells. It was, indeed, the only criterion then available, since selective dyeing was not yet used. But as Aschoff [2] pointed out, one cannot, on the basis of phagocytosis alone, mark out a special cell system, since probably all cells under the right conditions show their primitive power of phagocytosing and digesting foreign bodies.

Apart from Metchnikoff's work, the early history of the conception of what is now known as the reticulo-endothelial system is the history

* Submitted for publication, Sept. 6, 1928.

* From the Department of Bacteriology, Columbia University College of Physicians and Surgeons.

1. Metchnikoff, E.: Immunity in Infective Diseases, New York, G. P. Putnam's Sons, 1905.

2. Aschoff, L.: Ergebn. d. inn. Med. u. Kinderh. **26**:1, 1924.

of attempts at vital staining. As early as 1869, Ponfick [3] injected mercury into the lymph sacs of frogs and studied the subsequent distribution of the metal. He failed, however, to differentiate between phagocytosis of particles of the mercury and vital dyeing, which occurs only with colloidal solutions, so that the metal was found in parts of the body that contain none of the reticulo-endothelial system as it is now recognized.

The first to stain the reticulo-endothelial system selectively was Ribbert.[4] He used a colloidal solution of lithium carmine, and showed that after the injection of this material the whole body did not stain, but certain cells only, and that these cells were the same as those that could be filled with hemosiderin and fat.

The study of this cell system received a great impetus with the first use of Ehrlich's vital dyes, particularly pyrrol blue, by Goldmann.[5] This worker was able to correlate the observations of Marchand,[6] Maximow [7] and Renaut,[8] and to show that the large phagocytic cells that they had designated by various names were one and the same. Goldmann was also the first to point out a fact that has come more and more into prominence of late years, namely, that this system plays a rôle in normal metabolism, particularly of glycogen and fat.

Kiyono [9] continued the work on some of the problems that Goldmann raised, especially that as to the origin of the tissue macrophages, or, as he called them, the "histiocytes," in inflammatory processes. At the same time, Aschoff and Landau [10] first used the phrase "reticulo-endothelial system" in a study that they made on the relation of this system to cholesterol. Kiyono, with his pupils, in recent years established the comparative anatomy of the reticulo-endothelial system in all the classes of vertebrates.

Since 1914, a vast literature on the reticulo-endothelial system has grown up, and with it has come a realization of the importance of these cells, not only in pathologic conditions, but in normal metabolism in which their function is probably even more fundamental. Relatively complete summaries of this work are to be found in the reviews of Aschoff,[2] Oberling,[11] Krumbhaar [12] and Sacks.[13]

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3. Ponfick, E.: Virchows Arch. f. path. Anat. **48**:1, 1869.
4. Ribbert, H.: Ztschr. f. allg. Physiol. **4**:201, 1904.
5. Goldmann, E.: Beitr. z. klin. Chir. **64**:192, 1909.
6. Marchand, F.: Sitzungsb. d. Gesellsch. z. Beford. d. ges. Naturw. zu Marb. **6**:105, 1897.
7. Maximow, A.: Arch. f. mikr. Anat. **67**:680, 1906.
8. Renaut, J.: Arch. d'anat. micr. **9**:495, 1907.
9. Kiyono, K.: Die Vitalekarminspeicherung, Jena, Gustav Fischer, 1914.
10. Landau, M.: Ber. d. Naturforsch. Gesellsch. zu Freiburg, 1913, vol. 20.
11. Oberling, C.: Ann. d'anat. path. **1**:87, 1924.
12. Krumbhaar, E. B.: Internat. Clin. **2**:280, 1925.
13. Sacks, B.: Physiol. Rev. **6**:504, 1926.

RECTICULO-ENDOTHELIAL MORPHOLOGY

Aschoff's definition of the reticulo-endothelial system divides the cells into several categories, the criterion being the intensity with which they take vital dyes in colloidal solution. Thus, four groups are formed, which constitute the reticulo-endothelial system in the wider sense. In a classification slightly modified from that of Aschoff (1924), these groups are: (1) the recticulum cells of the spleen; cortex and medulla strands of the lymph glands; and the other lymphatic tissues; (2) the reticulo-endothelium of the lymph sinuses, blood sinuses, spleen, Kupffer cells, bone marrow capillaries, suprarenal cortex and hypophysis; (3) the histiocytes of the connective tissues (clasmatocytes or tissue macrophages), and (4) the splenocytes and vitally staining monocytes (endothelial leukocytes and blood histiocytes), which arise from the reticulo-endothelium (group 2) and from the histiocytes (group 3).

The cells in groups 2 and 3 stain the most quickly and intensely; those in groups 1 and 4 show somewhat less avidity for the dyes, but their capacity for staining is far greater than that of the fibroblasts and that of the vascular endothelium. The two latter types of cells store dye only slightly after intense and long continued staining of the animal.

The complex interrelations of all these cells cannot be discussed here. They are admirably considered in the reviews mentioned, and also in the articles of Maximow [14] and Foot,[15] which deal specifically with these relations.

MALARIA

From a careful study of bird malaria, Ben-Harel [16] concluded that the destruction of the parasites is due to the activity of the fixed tissue cells. This process seems to take place principally in the spleen, in which, at the height of the infection, the fixed cells of the endothelial lining are swollen with pigment and parasites. Free parasites are also numerous around the detached monocytes. The blood picture also shows significant changes. The number of monocytes increases directly with the number of parasites, thus showing a response on the part of the reticulo-endothelial apparatus. The actual destruction of parasites by mononuclears in the blood stream appears to be a rare process; however, Ben-Harel, who observed only a single instance of such phagocytosis, stated that the intracellular digestion is so rapid that it cannot often be found.

A similar phagocytosis and destruction of the parasites of malaria in birds had been earlier observed by MacCallum.[17] Thomson,[18] from a

14. Maximow, A.: Physiol. Rev. **4**:533, 1924.
15. Foot, N. C.: Anat. Rec. **30**:15, 1925.
16. Ben-Harel, S.: Am. J. Hyg. **3**:652, 1923.
17. MacCallum, W. G.: J. Exper. Med. **3**:104, 1898.
18. Thomson, D.: Ann. Trop. Med. **5**:83, 1912.

study of a large number of cases of malaria in man, concluded that "mononuclear leukocytes, especially the large variety, are undoubtely the soldiers for defense," in this condition. He observed further that during treatment with quinine, accompanied by a decrease in the number of parasites, there is a corresponding increase in the number of mononuclears; and in contrast with the observations on malaria in birds, he pointed out "that in malarial fever the curve representing the percentage of total mononuclear leukocytes is the exact reverse of the temperature curve."

James,[19] however, considered that the actual appearance in the blood stream of large macrophages (15 microns or more in diameter) is diagnostically more important than any change in leukocytic proportions. Nevertheless, both phenomena are the expression of a response on the part of the reticulo-endothelial mechanism. With still more severe infections, the large "endothelial leukocytes" appear in the blood. Anderson [20] believed that their presence is a sign of a malarial infection of the gravest character, and it is, indeed, evidence of a sharp attack on an important protective mechanism. A similar increase in the large mononuclears in malaria has been reported by Schilling.[21] In one case, he found that 33 per cent were monocytes, and in other cases that frequently from 12 per cent to 30 per cent were monocytes. Christophers and Stephens [22] considered a mononuclear count of 15 per cent or higher as evidence of active malaria. Schilling showed that the cells that are numerically increased in the blood stream during malarial infections correspond with the large monocytes of the spleen, which have probably freed themselves into the blood stream. Histologically, the spleen presents a proliferation of these cells.

In a comprehensive study of malignant malaria, Gaskell and Miller [23] found phagocytosis of the parasites by what they described as the "branched supporting cells" of the spleen and by stellate cells in the liver. The former type of cell is probably the reticulum cell and the latter the Kupffer cell.

In this connection, the observations of McLay [24] are of interest. He studied cultures of *Plasmodium falciparum* and noted that there is a

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19. James, S. P.: Malaria at Home and Abroad, London, William Wood & Company, 1920.

20. Anderson, W. K.: Malarial Psychoses and Neuroses, London, Oxford University Press, 1927.

21. Schilling, C., in Mense, C.: Handbuch der Tropenkrankheiten, Leipzig, Johan Ambrosius Barth, 1924.

22. Christophers and Stephens, cited by McLay, K.: J. Roy. Army M. Corps **38**:93, 1922.

23. Gaskell, J. F., and Miller, W. L.: Quart. J. Med. **13**:381, 1920.

24. McLay, K.: J. Roy. Army M. Corps **38**:93, 1922.

pronounced tendency for the infected erythrocytes to collect about and adhere to the large mononuclears. He confirmed previous workers in the observation that the mononuclears are increased in number as are also their parent cells, the endothelial phagocytes of the internal organs. The clumping of the infested erythrocytes around the mononuclears may possibly be the result of a positive chemotaxis, and the increase in the number of the mononuclear cells in the culture films during the process of cultivation suggests that they may be connected with the dying out of the parasites. He further concluded that these cells are an important part of the body's defenses against *Plasmodium falciparum*. Commenting on this work, Wenyon [25] pointed out that it is probable that in infections with *Plasmodium falciparum*, which have been latent for a long period, the cycle of development is continuous in the vicinity of the cells to which the parasites tend to cling, namely, in the spleen and the bone marrow.

Much of the work that has been reviewed here suggests the possibility that immunity to malaria, slight though it be, arises from the activity of the reticulo-endothelial system. At least, there can be no doubt that the cells of this system play an outstanding part in the obvious defense processes of the body, such as phagocytosis; it is to them that one would be inclined to look for the origin of the less easily analyzed phenomena of immunity to malaria.

Recently, Ruge [26] made the interesting suggestion that the constant presence of malarial pigment in the cells of the reticulo-endothelial system prevents the production of immunity to malaria. The pigment is thought to act as a "blocking" material, analogous to india ink or trypan blue. Such a hypothesis must be received with caution, since experimental results from a blockade are well known to be extremely variable, particularly in cases in which the formation of antibodies is involved.

A diagnostic test for malaria that indirectly involves the reticulo-endothelial system was devised by Kingsbury.[27] He pointed out that this system normally breaks hemoglobin into bilirubin and that the amount of bilirubin is increased in cases in which the destruction of erythrocytes is increased, as in malaria. He found that, under treatment with quinine, the amount of bilirubin in the serum decreases. Kingsbury advocated the determination of the amount of bilirubin in the serum as a test for malaria.

None of the other sporozoan parasites found in man has been noted in connection with the reticulo-endothelial system. Observations have been made, however, that certain of the hemogregarines of the lower

25. Wenyon, C. M.: Protozoology, London, William Wood & Company, 1926.
26. Ruge, R.: Med. Welt **1**:2, 1927.
27. Kingsbury, A. N.: Tr. Roy. Soc. Trop. Med. & Hyg. **20**:359, 1927.

mammals pass at least part of their life cycle in the cells of this system. These observations may be briefly reviewed. Patton,[28] in 1906, described a hepatozoon within the mononuclear leukocytes of an Indian palm squirrel. In infected animals, the mononuclear leukocytes averaged 60 per cent, while in normal, noninfected animals these cells averaged 28 per cent. The proportion of mononuclears was higher in the more heavily infected animals. Christophers [29] and Wenyon [30] found that the schizogony cycle of *Hepatozoon canis* takes place in mononuclear cells of the spleen and the bone marrow, while the gametocytes occur in the circulating mononuclears. The blood monocytes harbor the gametocytes also in *Hepatozoon perniciosum* infestations of the rat, according to Kasuma, Kasai and Kobayashi.[31] The latter form, which was reported by Miller [32] in 1908, was described as having schizonts exclusively in the liver cells. Wenyon,[25] however, was of the opinion that the schizonts may in reality be in the Kupffer cells. If so, the entire mammalian cycle occurs in cells of the reticulo-endothelial system.

KALA-AZAR

Kala-azar is apparently an example of a primary and chronic infection of the reticulo-endothelial system. In the earliest careful description of the disease, Christophers [33] emphasized the intracellular position of the parasites. They were present in the endothelial cells or macrophages not only in the liver and the spleen, but most strikingly in the intestinal wall, where they occupied the interior of the macrophages, in the granulation tissue which had replaced the mucosa. He also pointed out the characteristic infiltration of various organs with macrophages, particularly the liver, the spleen and the bone marrow. These changes were recently studied by Meleney,[34] who found that the proliferation and infiltration of macrophages in these organs may be so great as to fill the greater part of each of them. In extreme cases, the connective tissue clasmatocytes of almost all the organs and tissues are infested.

Further work by two English investigators, Shortt [35] and Perry,[36] clearly showed kala-azar to be essentially a disease of the reticulo-endothelium. Shortt, who studied the disease experimentally in two monkeys,

28. Patton, W. S.: Scient. Mem. Med. Off. India, Calcutta, 1906, no. 24.
29. Christophers, S. R.: Scient. Mem. Med. Off. India, Calcutta, 1906, no. 26.
30. Wenyon, C. M.: Parasitol. **4**:273, 1911.
31. Kasuma, S.; Kasai, K., and Kobayashi, R.: Kitasato Arch. Exper. Med. **3**:103, 1919.
32. Miller, W. S.: Bull. Hyg. Lab., U. S. P. H. S., 1908, no. 46.
33. Christophers, S. R.: Scient. Mem. Med. Off. India, Calcutta, 1904, nos. 8 and 11.
34. Meleney, H. E.: Am. J. Path. **1**:147, 1925.
35. Shortt, H. E.: Indian J. M. Research **11**:186, 1923-1924.
36. Perry, H. M.: J. Roy. Army M. Corps. **39**:323, 1922.

stated that the parasites are confined to one special tissue of the body, and this tissue is endothelium. Perry investigated intestinal infections with *Leishmania donovani* and found that the interiors of many villi in the small intestine were replaced and filled with large macrophages loaded with parasites. He believed that these macrophages arise from the lymphatic endothelium of the central lacteals in each villus.

Important contributions have recently been made to the subject of kala-azar in its relation to reticulo-endothelium by a group of workers in Peking. Young, Smyly and Brown [37] discovered that the Chinese hamster (*Cricetulus griseus*) is an excellent animal for use in the experimental production of this disease. In their brief report, they made record that the enlarged spleen is the only gross pathologic change that this animal shows. Later, Meleney, in his thoroughgoing study of kala-azar in the hamster and the monkey, as well as in man, reported that the two main features of the disease in all these animals are: (1) an extensive proliferation of endothelial cells in the liver, the spleen and the bone marrow (that is, the reticulo-endothelium) and (2) the formation of large islands of such cells (clasmatocytes) in these organs. These cells are selectively infested by *Leishmania donovani.*

The next contribution was made by Hu and Cash,[38] who by means of vital and supravital staining proved conclusively the reticulo-endothelial character of the infested cells. When they injected china ink, which has a specific affinity for this system, into an animal infected with *Leishmania,* they found that the ink was taken up by the cells that contained the parasites. The infested cells were obtained for supravital staining by puncture of the spleen, and their reaction to the dye showed that they were clasmatocytes.

They also noted the interesting fact that large numbers of the parasites are to be found in clasmatocytes lying in various layers of the skin. In another report,[39] they showed that much the same condition is present in the human skin, in which again it is the clasmatocytes that contain the parasites.

Further evidence of the involvement of the reticulo-endothelium in man is found in a study of 400 cases of visceral leishmaniasis in Spaniards made by Pittaluga.[40] He concluded that the disease is one of blockage of the reticulo-endothelial apparatus. To this blockage, he attributed the symptoms of the disease: anemia, leukopenia, splenomegaly and hepatomegaly and cutaneous hemorrhages.

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37. Young, C. W.; Smyly, H. J., and Brown, C.: Proc. Soc. Exper. Biol. & Med. **21**:357, 1924.

38. Hu, C. H., and Cash, J. R.: Proc. Soc. Exper. Biol. & Med. **24**:469, 1927.

39. Cash, J. R., and Hu, C. H.: Kala-Azar; Demonstration of Leishmania Donovani in the Skin and Subcutaneous Tissue of Patients; Possible Relation to the Transmission of the Disease, J. A. M. A. **89**:1576 (Nov. 5) 1927.

40. Pittaluga, G.: Arch. f. Schiffs- u. Tropen-Hyg. **21**:340, 1927.

Not all workers, however, have found *L. donovani* exclusively in the cells of this system. Laveran and Havet [41] described the liver cells of an experimentally infected dog as more heavily infested than the Kupffer cells. Shortt could not confirm this in his work on monkeys, and such heavy infestation has not been found by other workers, although a slight infection of liver cells has been reported elsewhere, as, for example, in Meleney's paper. *Leishmania* is also found occasionally in polymorphonuclear cells. These occasional and, in part, unconfirmed results do not weaken the main trend of the other observations; namely, that kala-azar is a disease which primarily attacks the reticuloendothelial system.

As might be expected from the nature of the disease, the numerical proportions of the blood cells are changed in kala-azar. Schittenhelm [42] described a leukopenia with a considerable increase in the proportion of mononuclears. The cell percentages vary considerably with different authors. Knowles [43] found the percentage of these cells ranging from 6 to 40. Rogers [44] found mononuclear counts of over 12 per cent in 69 per cent of the cases that he studied, while Donovan [45] obtained an average of 23 per cent.

The protozoons classed as *Leishmania,* other than *L. donovani,* show a similar tendency to invade the macrophages. The first observation of tissue macrophages in the oriental sore seems to have been made by Riehl [46] in 1886, although the parasites themselves (*L. tropica*) were seen by Cunningham [47] in the previous year. The first thorough report on the cells did not appear until 1903; in that year Wright [48] noted that the great majority of the organisms occur in the lesions within cells that are undoubtedly clasmatocytes. The principal part of the infiltration that he observed was due to cells of this type; this has been confirmed by numerous workers. Interesting cases of dermal leishmanoid infections that appeared in patients undergoing treatment for kala-azar were reported by Shortt and Brahmachari.[49] The parasites (*L. donovani*) occurred subcutaneously within masses of cells, which, from the careful descriptions and the photomicrographs, were, without doubt,

41. Laveran, A., and Havet, J.: Bull. Soc. de path. exot. **10**:396, 1917.

42. Schittenhelm, A.: Handbuch der Krankheiten des Blutes, Berlin, Julius Springer, 1925.

43. Knowles, R.: Indian J. M. Research **8**:140, 1920.

44. Rogers, L.: Fevers in the Tropics, London, H. Frowde, Hodder & Stoughton, 1908.

45. Donovan, C., cited by Schittenhelm (footnote 42).

46. Riehl, G.: Vrtljschr. f. Derm. u. Syph., 1886, p. 805.

47. Cunningham, D. D.: Scient. Mem. Med. Off. India, Calcutta **1**:21, 1885.

48. Wright, J. H.: J. M. Research **10**:472, 1903.

49. Shortt, H. E., and Brahmachari, U. N.: Indian J. M. Research **12**:463, 1925.

tissue macrophages. Recently, Llambias and Mosto [50] pointed out that in a case of American dermal leishmaniasis the mononuclear cells were the most prevalent type.

EXPERIMENTAL TRYPANOSOMIASIS

It is becoming increasingly evident that in many experimental infections with trypanosomes, the reticulo-endothelial system is not directly involved. Laveran and Mesnil [51] described an intraperitoneal phagocytosis of *T. lewisi* by large mononuclear cells; but their observations could not be confirmed by MacNeal [52] nor by Manteufel.[53] Dwijkoff,[54] in a careful hematologic study of guinea-pigs infected with *T. brucei*, never observed a mononuclear count greater than 6 per cent, and concluded that a reaction of the reticulo-endothelial system had not occurred. Linton,[55] working with splenectomized guinea-pigs infected with *T. equiperdum*, did not find any differences in respect to incubation period or length of life between these animals and nonsplenectomized controls, showing that the absence of this important portion of the apparatus did not have any effect on the course of the disease.

In some instances, however, notably in the results of Rosenthal and of Taliaferro, which will be discussed later, this apparatus has been found responsible for immunity in infections with trypanosomes, although only indirectly.

The Trypanocidal Action of Serum from Human Beings.—Rosenthal began with the observation of Laveran [56] that serum from normal human beings is trypanocidal when injected into mice infected with *T. brucei*, *T. evansi* or *T. equiperdum*. In collaboration with Nossen [57] and later with Kreuger,[58] Rosenthal noted that in the case of certain severe disturbances of the liver, such as cancer with icterus, the trypanocidal power of serum from human beings, as shown by injection into infected mice, is weakened and may even disappear. From their work, they concluded that the trypanocidal substance is a secretion of the liver. This conclusion was confirmed by Peutz,[59] Neumark and Pagorschelsky [60] and others.

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50. Llambias, J., and Mosto, D.: Compt. rend. Soc. de biol. **95**:823, 1926.
51. Laveran, A., and Mesnil, F.: Ann. de l'Inst. Pasteur **15**:673, 1901.
52. MacNeal, W.: J. Infect. Dis. **1**:517, 1904.
53. Manteufel: Arb. a. d. k. Gsndhtsamte **33**:46, 1909.
54. Dwijkoff, P.: Folia haemat. **33**:1, 1926.
55. Linton, R. W.: Unpublished experiments.
56. Laveran, A.: Compt. rend. Acad. d. sc. **134**:735, 1902.
57. Rosenthal, F., and Nossen, H.: Berl. klin. Wchnschr. **58**:1093, 1921.
58. Rosenthal, F., and Kreuger, M.: Berl. klin. Wchnschr. **58**:382, 1921.
59. Peutz, J. L. A.: Nederl. Tijdschr. v. Geneesk. **66**:1544, 1922.
60. Neumark, E., and Pagorschelsky, H.: Ztschr. f. Kinderh. **40**:535, 1925.

Later research by Rosenthal and Freund [61] repeated the earlier observations and added several important points to them. The trypanocidal substance is present in the euglobulin and pseudoglobulin fractions of serum from man. It does not have antigenic power in rabbits and mice; that is, an antitrypanocidal substance is not formed by the injection of serum from human beings into these animals. The repeated injection of small amounts of this serum into a mouse renders a subsequent injection for protective purposes ineffectual. Since the repeated injections do not cause the formation of an antitrypanocidal substance and from the further consideration that serum from human beings is inactive in vitro, Rosenthal and Freund were led to the hypothesis that this serum does not act directly to kill the trypanosomes, but is first activated by some element of the mouse body. Thus, the ineffectiveness of serum from human beings in mice into which it has been injected repeatedly is due to an exhaustion of the mechanism for its activation. As a corollary to this hypothesis, one must assume that the natural immunity which man shows against animal trypanosomes is not due to the trypanocidal action of his serum, as was once supposed, but depends on some other mechanism.

In a final report, Rosenthal and Spitzer [62] completed the work in a study of the mechanism whereby serum from human beings is activated in mice. They showed first that treatment of animals with thorium-X resulting in almost total destruction of the circulating leukocytes, did not prevent a complete activation of this serum. Their further experiments were on the activity of the reticulo-endothelial system. In mice treated with saccharated iron oxide, which is taken up selectively by the cells of this system, they obtained an inconstant but often pronounced lowering of the trypanocidal power, followed in some cases by the death of the animal. The saccharated iron oxide itself did not render serum from human beings incapable of being activated. In other experiments, they extirpated the spleen, which in mice forms a higher proportion of the reticulo-endothelial system than in other animals, and found that little activation of the serum from man took place. That is, the splenectomized animals frequently died of the trypanosome infections. The controls given similar doses of trypanosomes and of the serum were completely protected. Finally, it was found that blocking, combined with splenectomy, was invariably fatal.

From these experiments, the authors concluded that the serum of human beings, which is inactive in vitro, becomes trypanocidal in the mouse through its activation by the reticulo-endothelial system. These important researches have clearly demonstrated the importance of the

61. Rosenthal, F., and Freund, R.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:48, 1923.

62. Rosenthal, F., and Spitzer, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **40**:529, 1924.

tissues in a certain type of protection against protozoan infections, namely, protection due to an activation of a foreign substance, whether serum or drug, by the body cells.

The results of several earlier experimenters find their explanation in this work of Rosenthal. Thus Laveran and Mesnil [63] noted that the usual energetic action of the serum of human beings against *T. brucei* in mice failed after several injections, and the animals succumbed. The same phenomenon was observed by Jacoby [64] and by Leboef.[65] In the light of Rosenthal's work, it is clear that by means of their repeated injections these workers had exhausted the activating power of the mouse reticulo-endothelium for the serum of man.

Reticulo-Endothelium and the "Reaction-Product" of Taliaferro.—In a series of papers, Taliaferro [66] described a new type of resistance in rats infected with the nonpathogenic *T. lewisi.* This resistance manifests itself in an inhibition of mitosis, so that the organisms after several days cease to divide. Their eventual disappearance, Taliaferro believed, is due to lysis, a phenomenon entirely separate from the inhibition of reproduction. The "reaction product" that inhibits reproduction may be transferred in the serum from an infected rat to a normal rat, and prevent the organisms from showing any reproduction in the latter animal.

The existence of this property was confirmed by Coventry [67] and by Regendanz and Kikuth.[68] The former studied particularly the titer of the "reaction product" at various stages during the infection and found that, while it could not be demonstrated on the fifth day of the infection when reproduction had begun to decrease, it appeared explosively on the sixth day in large amount and gradually increased until about the thirty-fifth day, when it again diminished.

Interesting from the present point of view is the confirmation of Taliaferro's results by Regendanz and Kikuth. They splenectomized rats and infected them with *T. lewisi.* In these animals, numerous dividing forms could be found for two or three days longer than in nonsplenectomized controls, and in some cases the infections terminated fatally, without the appearance of any product inhibiting reproduction. Hence, they believed that the spleen is the important site of the formation of Taliaferro's "reaction product," and, on the basis of the work of others on the formation of antibodies, concluded further that the reticulo-endothelial apparatus is involved.

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63. Laveran, A., and Mesnil, F., cited by Schilling, in Kolle and Wassermann: Handb. d. pathogenen Mikroorganismen, Jena, Gustav Fischer, 1927, vol. 8, p. 95.
64. Jacoby, M.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**:689, 1909.
65. Leboef, A.: Ann. de l'Inst. Pasteur **25**:882, 1911.
66. Taliaferro, W. H.: Am. J. Hyg. **3**:104, 1923; J. Exper. Med. **39**:171, 1924.
67. Coventry, F. A.: Am. J. Hyg. **5**:127, 1925.
68. Regendanz, P., and Kikuth, W.: Centralbl. f. Bakteriol. **103**:271, 1927

The Reticulo-Endothelial System and Chemotherapeutic Activity.—It has been known for years that many chemotherapeutic substances have a much greater activity against protozoa in vivo than in vitro, some of them indeed being without parasiticidal action in the test tube. For example, Oettinger [69] found that while solutions of neoarsphenamine in dilution of 1 : 3,000 are inactive in vitro, in the body, in which their concentration may be only 1 : 70,000 or 1 : 80,000, they show a strong parasiticidal action.

The exact mode of action of chemotherapeutic substances is still a matter of experiment and controversy. It is agreed, however, that with many drugs the body does not take a passive part, but either elaborates the drug into an effective parasiticidal substance, or is stimulated by it to form or to set free parasiticidal antibodies. The experiments of Schilling and Jaffé [70] pointed to the latter possibility. Three hours after the injection of arsenophenylglycine into a rabbit infected with *T. brucei*, 1 cc. of its serum, which had previously been inactive, was able to lengthen the period of incubation in a mouse infected with the same organism to thirteen days and to prolong its life to the sixteenth day. They believe that the circulating drug itself does not cause this increased trypanocidal power, for 0.5 cc. of rabbit serum taken nine days after the last injection of the drug protected a mouse. They account for the rapid appearance of the antibodies in the rabbit's blood on the hypothesis that these substances are already formed in the tissue cells and are released by the action of the arsenophenylglycine.

While discrepancies between activity in vitro and that in vivo have long been recognized, it is only recently that a closer analysis, from a cellular point of view, has been attempted. Studies in this direction were reported in three papers, which appeared almost simultaneously, by Jungeblut,[71] Feldt and Schott [72] and Kritschewsky and Meersohn.[73] The methods in all were essentially the same. White mice were splenectomized, or were given injections of some kind of "blocking" material, such as saccharated iron oxide or india ink; or were treated in both ways. The animals were then infected, together with normal controls, with the spirochete of recurrent fever or with *T. brucei*. In some of the experiments of Feldt and Schott, a streptococcus was used. After infection, they were treated with various chemotherapeutic substances,

69. Oettinger, J.: Ztschr. f. klin. Med. **103**:546, 1926.

70. Schilling, C., and Jaffé, J.: Arch. f. Schiffs- u. Tropen-Hyg. **13**:525, 1909.

71. Jungeblut, C. W.: Ztschr. f. Hyg. u. Infektionskrankh. **107**:357, 1927.

72. Feldt, A., and Schott, A.: Ztschr. f. Hyg. u. Infektionskrankh. **107**:453, 1927.

73. Kritschewsky, I. L., and Meersohn, I. S.: Ztschr. f. Immunitatsforsch. u. exper. Therap. **47**:407, 1926.

and the subsequent course of the infection was compared with that in the controls. In every case, it was found that the splenectomized and blocked mice showed severer infections and a mortality much higher than the control mice. Jungeblut found a death rate of 62 per cent in the splenectomized and blocked animals as compared with one of 11 per cent in the controls. Kritschewsky and Meersohn obtained figures of 75 per cent and 10 per cent, respectively. Jungeblut concluded that "the full action of chemotherapeutic substances in protozoan infections of mice appears in general to depend upon the presence of an intact reticulo-endothelial system." The conclusions of the other authors were essentially the same.

In subsequent studies, Kritschewsky [74] tested a large series of drugs in a way similar to that described. Without exception, the activity of the drugs was lessened or abolished after splenectomy, either alone or combined with blocking. This worker's view is that, since the drug cannot enter the reticulo-endothelial cells, it is rapidly excreted. The intracellular occurrences are not known, but Kritschewsy believed it is possible that there a metamorphosis of the drug into its active form takes place.

Using similar materials and technic, Kolpikow [75] tested the response of mice to drugs at varying intervals after splenectomy. He concluded that there was a gradual replacement of the spleen by other cells in the function of drug activation, since the longer after splenectomy the dose was given, the better was the response. After about fifty days, the amount of activation was almost as good as in nonsplenectomized animals.

Kligler and Weitzman [76] discovered an important further interaction between a drug and the reticulo-endothelial apparatus. Animals cured by Bayer 205 of an otherwise fatal infection with *T. evansi* developed a resistance to reinfection, which lasted about five months. They believed that this resistance is cellular in character, because humoral antibodies could not be demonstrated and because blocking of the reticulo-endothelial system with oil caused a disappearance of the resistance.

Later Kligler [77] reported that animals cured and made resistant to *T. evansi*, as in the earlier work, are also insusceptible to reinfection with *T. gambiense* for about the same period.

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74. Kritschewsky, I. L.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**: 506, 1927.

75. Kolpikow, N. W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **48**:182, 1926.

76. Kligler, I. J., and Weitzman, I.: Proc. Soc. Exper. Biol. & Med. **23**:355, 1926.

77. Kligler, I. J.: Ann. Trop. Med. **22**:21, 1928.

SUMMARY

While conclusions are not to be drawn from this review, it is apparent that as a more thorough insight into the course of protozoan infections has been gained, the tissue cells of the host have assumed a correspondingly greater importance. A direct action of these cells is shown in malaria and in kala-azar and an indirect action in some of the experimental infections with trypanosomes and in chemotherapeutic action. Whether the responses of the animal body to protozoan infections will prove to be qualitatively different from those to the bacterial diseases, which have been much more deeply investigated, is a question that future research will decide. There is evidence, however, especially in the work of Taliaferro and of Rosenthal, that different types of response do occur in protozoan infections.

Notes and News

University News, Promotions, Registrations and Appointments.—At Columbia University, New York, Frederick B. Humphreys has been made associate professor of bacteriology, and Maurice N. Richter and Theodore F. Zucker, assistant professors of pathology.

In the School of Medicine, Western Reserve University, Cleveland, Alan Moritz has been promoted to be assistant professor of pathology; David Seecof has been appointed assistant professor of pathology, and LaVerne Barnes, senior instructor in bacteriology and hygiene; Howard T. Karsner, professor of pathology since 1914, has been given the additional title of director of the Institute of Pathology which has just been completed.

Burrell O. Raulston, at one time instructor in pathology at Rush Medical College, Chicago, has been appointed professor of medicine in the University of Southern California.

Frederick Eberson has been appointed director of the laboratories of the Mount Zion Hospital, San Francisco.

At the University of Cincinnati, Pearl M. Zeek has been made instructor in pathology. Pearl M. Zeek and Irving H. Schroth have been appointed assistant visiting pathologists to the Cincinnati General Hospital.

In the School of Medicine, St. Louis University, William D. Collier has been made director of the department of pathology and John R. Roberts has been promoted to senior instructor in pathology.

Detlev W. Bronk has been appointed Johnson professor of biophysics in the University of Pennsylvania School of Medicine and director of the Johnson Foundation for Research in medical physics.

Aldo Perroncito, professor of general pathology in the University of Pavia since 1921, succeeding his uncle, Camillo Golgi, has died at the age of 46.

Edward C. Streeter has been appointed visiting professor of the history of medicine in the medical school of Yale University.

John F. Kessel has been appointed associate professor of bacteriology and parasitology in the school of medicine of the University of Southern California.

At the University of Chicago, Isidore S. Falk has been promoted to a full professorship in bacteriology and hygiene.

After about thirty-two years of service, Timothy Leary has resigned as professor of pathology, bacteriology and medical jurisprudence in Tufts College Medical School, Boston.

Allan W. Blair has been appointed instructor in pathology and bacteriology in the University of Alabama.

Veranus A. Moore, dean of the college of veterinary medicine, concludes this year a teaching career of thirty-three years at Cornell University. He was a member of the first veterinary faculty as professor of veterinary pathology and bacteriology in 1896, and in 1908 became dean of the college.

Kiyoshi Hosoi, recently of the department of physiology, Mayo Foundation, Rochester, Minn., has been appointed senior Littauer fellow in pathology at the Albany Hospital and Medical College; and Edward H. Crosby of the department of surgery, University of Chicago, junior Littauer fellow in pathology.

Yolande de la Pasture, instructor in pathology at the Albany Medical College, has resigned to accept a residency in pediatrics at the Boston Dispensary, Boston, Mass.

Arthur H. Dodge, ex-Lieutenant Commander, U. S. Navy, and pathologist at the Grasslands Hospital, Valhalla, N. Y., has died at the age of 51.

The medical fellowship board of the National Research Council has made the following reappointments for the year 1929-1930: Simon Dworkin, physiology; Stephen J. Maddock, experimental surgery; Kenneth I. Melville, pharmacology

and physiology; Valy Menkin, physiology; David McK. Rioch, neurophysiology, and Ethel D. Simpson, physiology. New appointments are: Edgar V. Allen, internal medicine; Eric G. Ball, physiological chemistry; Claude H. Forkner, pathology and clinical investigation; Emidio L. Gaspari, bacteriology and immunology; Arthur K. Koff, obstetrics; Milton Levy, biochemistry; Ava J. McAmis, physiological chemistry; Leone McGregor, pathology; Charles Midlo, anatomy, and Bruce Webster, internal medicine.

The Rockefeller Institute for Medical Research announces the following appointments and promotions to the scientific staff. Associates appointed are: Albert P. Krueger, A. L. Patterson and Oskar Seifried. Assistants are: Alf S. Alving, Frank H. Babers, Bernard Benjamin, George P. Berry, Robert T. Dillon, Samuel E. Hill, William H. Kelley, Franklin R. Miller, Clara Nigg, Merritt P. Sarles, Maxwell P. Schubert, Mark P. Schultz, Albert B. Scott, J. Murray Steele, Jr., Philip G. Stevens, Bettina Warburg and Bruce K. Wiseman. Assistants who are made associates are: Lawrence R. Blinks, Louis A. Julianelle, Philip Levine, John B. Nelson, Theodore Shedlovsky and Harold J. Stewart.

Ralph E. Miller, Hanover, N. H., and Harold C. Thornton, Ferrum, Va., have been assigned as fellows of the Mayo Foundation, Rochester, Minn., and will major in pathology.

Burdick Research Award.—Walter M. Simpson, director of the diagnostic laboratories of the Miami Valley Hospital, Dayton, Ohio, was the first recipient of the Ward Burdick Research Award (gold medal) at the recent meeting of the American Society of Clinical Pathologists, at Portland, Ore., in recognition of his researches in tularemia and undulant fever. At the meeting of the American Medical Association, at Minneapolis, in 1928, Dr. Simpson was awarded the gold medal (class II) for his exhibit of the gross and microscopic changes in tularemia. The late Ward Burdick, of Denver, was instrumental in organizing the American Society of Clinical Pathologists eight years ago. He died in 1928. It is the purpose of the society to perpetuate his memory by the presentation of an annual research award to the member of the society who has made an outstanding contribution to medical research.

Committee on Gases in Refrigerators.—The American Medical Association has appointed the following committee to report on the danger of intoxication from the use of gases such as methyl chloride in household refrigerators: H. Gideon Wells, R. L. Thompson, Casey P. McCord, Yandell Henderson and Paul N. Leech.

Kober Medal.—The Kober medal of the Association of American Physicians for 1929 has been awarded to George R. Minot, Boston, for his work on the treatment of pernicious anemia.

Cooperative Research in Dental Physiology and Pathology.—The Rockefeller Foundation has made a grant to the medical school of Yale University toward the intensive study of the physiology and pathology of the teeth. Milton C. Winternitz is the chairman of the group of scientists in different fields in charge of the work.

New York Lying-In Hospital.—Frederick A. Hemsath has been appointed pathologist. He resigns as director of the Cattaraugus County Laboratory, New York.

American Society of Clinical Pathologists.—At the annual meeting in Portland, Ore., on July 8, James H. Black, Dallas, Texas, was made president, and Kenneth M. Lynch, Charleston, S. C., president-elect. Harry J. Corper, Denver, continues to be secretary-treasurer.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EXPERIMENTAL PERICARDITIS. GEORGE HERRMAN and J. H. MUSSER, Am. Heart J. **4**:268, 1929.

Various types of chronic fibrous pericarditis can be reproduced at will in dogs. The animals may show no pathologic clinical signs, and the electrocardiographic observations may be negative, but the fluoroscope will often reveal significant changes in the character and movements of the left border of the heart. The greatest degree of cardiac hypertrophy is found in those cases in which chronic mediastinal and peritoneal adhesions accompany the adhesive pericarditis. The feasibility of digital separation of pericardial adhesions and the prevention of reformation of adhesions have been proved, and clinical and pathologic evidence of benefit has been noted in animals.

PEARL ZEEK.

MYXEDEMA HEART. JACOB EASTMON HOLZMAN, Am. Heart J. **4**:351, 1929.

Myxedema heart is characterized by an enlargement of all four chambers, slow pulse rate, normal blood pressure and electrocardiographic changes. Two groups are recognized: those cases which respond to thyroid therapy, and those in which myxedema of long standing and other factors have produced permanent myocardial changes which do not permit a response to thyroid medication.

PEARL ZEEK.

THE DIAGNOSIS OF EARLY PREGNANCY THROUGH THE DETECTION OF FEMALE SEX HORMONE IN THE URINE. CHARLES MAZER and JACOB HOFFMAN, Am. J. Obst. & Gynec. **17**:186, 1929.

Carefully selected castrated mice (two for each test) were injected with 20 minims of urine for five consecutive intervals of two hours. The urine was obtained from pregnant and control nonpregnant women. The production of estrus-like changes in the vaginal smear of the mice, by the pregnant urine only, was considered as positive evidence of the presence of female sex hormone in the urine and diagnostic for pregnancy. The contradictory observations of Frank and Goldberg showing an absence of this hormone in the blood of early pregnancy are explained by Mazer and Hoffman by assuming that there is possibly an increased renal permeability for the hormone which depletes the blood of its presence, but later, when the placenta supplements the function of the corpus luteum of pregnancy, large quantities of sex hormone appear in the blood apparently more than the kidneys can filter through.

A. J. KOBAK.

RHYTHMIC VARIATIONS IN THE VASCULARITY OF THE UTERUS OF THE GUINEA PIG DURING THE ESTROUS CYCLE. J. E. MARKEE, Am. J. Obst. & Gynec. **17**:205, 1929.

Three methods were utilized in studying cyclic variations that occur in the guinea-pig uterus. The first method consisted in opening the abdominal cavity and studying the gross and microscopic changes of the uterus in situ; a wave of light area was seen every minute to spread over the red uterus from the horns down to the cervix and lasted about ten or fifteen seconds. The second method consisted in studying transplants of endometrial tissue in the anterior chamber of the eye. The transplanted tissue underwent vascular changes which varied between 0 and 50 per cent on the Talquiet hemoglobinometer. Kymographic records were made of the color changes by means of a graduated dial and a muscle lever. "These vascular changes are influenced by the time of the day, being at their lowest ebb

in the early morning, increasing both in speed and extent in the forenoon, decreasing again about noon, and reaching their height late in the evening. They are influenced by the stage of the estrous cycle, showing during proestrous until they disappear completely for four or five hours and then to reappear before the end of the period of heat." The third method consisted in inserting a speculum 4 mm. in diameter through the vagina and half way up one of the horns of the uterus. By this procedure the observations made by the first two methods were confirmed in that the endometrium changed from red to white and back again from every fifteen to twenty seconds during diestrum, but not during estrus. The author concludes that the vascular changes are a phenomenon of the capillaries and arterioles of the uterus and especially of the mucous membrane.

A. J. KOBAK.

EXPERIMENTAL ENDOMETRIOSIS. S. S. SCHOCHET, Am. J. Obst. & Gynec. **17:** 328, 1929.

The cyclic variations of the endometrium in situ and when transplanted into other organs were studied and described by Schochet, who first used rabbits and later only virgin female guinea-pigs. The vessels of the transplants showed periodic rhythmic contractions, which were described by Markee who collaborated with Schochet on this phase of the work. These rhythmic variations consisted of an alternate blanching and blushing of the uterus in situ, and when endometrial tissue was transplanted into the anterior chamber of the eye, further cyclic variations were noted in the alternate changes of color which varied with the time of the day as well as the time of the estrous period that it was observed. A Tallquist scale was used for studying the degree of the color changes which occurred during the pro-estrous period, disappeared during the estrous period, and reappeared shortly after the postestrous period began. The experimental transplants were divided as follows: Series 1 consisted of normal controls removed during the pro-estrous period and transplanted into the spleen, liver and subcutaneous tissue; a second group of these controls was removed at varying periods and transplanted into the anterior chamber of the eye. Series 2 consisted in an observation of transplanted endometrium after the tissues had been subjected to lipoid solvents. In series 3, the tissues were first subjected to solutions of iso-osmotic strontium chloride followed by a change into hypertonic salt solution, and then washing in Ringer's solution before transplanting into the anterior chamber of the eye.

A. J. KOBAK.

RELATION OF SPRUE TO PERNICIOUS ANEMIA. AMERICO SERRA, Am. J. Trop. Med. **9:**49, 1929.

Pernicious anemia and sprue are two distinct disease entities. Important points of differentiation between the two diseases are emaciation, lack of fat utilization and small liver in sprue spinal cord changes, achlorhydria and fever in pernicious anemia. The icteric index is high in uncomplicated cases of pernicious anemia, while that in cases of sprue ranges within normal limits. Nitrogen retention is usually absent in sprue although common in pernicious anemia. The blood picture in the two diseases is similar. A high color index, macrocytosis and leukopenia with relative lymphocytosis are common to sprue and pernicious anemia. Polychromatophilia, anisocytosis, poikilocytosis and basophilic stippling are more marked in pernicious anemia. Nucleated red cells are rare and the reticulated cell counts are lower in sprue. The blood picture of sprue is of a more aplastic type than that of pernicious anemia.

H. E. LANDT.

THE RELATION OF OVARIES AND TESTES TO CHOLESTEROL METABOLISM. F. S. RANDLES and A. KNUDSON, J. Biol. Chem. **82:**57, 1929.

Experiments are described showing that removal of the testes from male or the ovaries from female rats has no appreciable effect on the cholesterol content of the blood.

AUTHORS' SUMMARY.

THE NEPHROPATHOGENIC ACTION OF CYSTINE. G. J. COX, C. V. SMYTHE and C. F. FISHBACK, J. Biol. Chem. **82**:95, 1929.

Very young rats manifest acute toxic nephrosis when restricted to synthetic diets containing from 0.3 to 0.9 per cent of the sulphur-containing amino-acid, cystine. Survival of the period of acute nephrosis appears to be associated with the development of a tolerance for the substance. Older rats are insusceptible.

ARTHUR LOCKE.

THE RÔLE OF THE PHOSPHOLIPIDS OF THE INTESTINAL MUCOSA IN FAT ABSORPTION. R. G. SINCLAIR, J. Biol. Chem. **82**:117, 1929.

The transformation of absorbed fatty acid into phospholipid may be an essential step in the resynthesis of neutral fat within the epithelial cells of the intestinal mucosa.

ARTHUR LOCKE.

THE FATE OF COLLOIDAL IRON ADMINISTERED INTRAVENOUSLY. CYRIL J. POLSON, J. Path. & Bact. **32**:247, 1929.

The distribution in the liver of an excess of iron, resulting from intravenous administration, was observed over a period of fourteen months, and the paths of the iron are described. The distribution and redistribution of iron in the organs are described. Iron held by the lungs is essentially a foreign substance and is transferred principally to the liver. It is suggested that the path of the iron in the lung is by way of the spleen. Iron is probably excreted by the cecum and the kidney, while part of the excess of iron in the liver is transferred to the lymphatic glands and remains in the body for some time.

AUTHOR'S SUMMARY.

EXPERIMENTAL ARTERIOSCLEROSIS. R. MANCKE, Arch. f. exper. Path. u. Pharmakol. **141**:228, 1929.

Mancke made a comparative study of the effects on the aorta of rabbits of certain alliphatic aldehydes, lactates, tartrates and irradiated ergosterol, with all of which Oswald Loeb had claimed it possible to cause arteriosclerosis in the rabbit. The work reported is essentially a repetition of Loeb's, but is based on a larger number of experiments. The compounds used and the daily dose per kilogram of body weight were formaldehyde bisulphide, 0.5 Gm.; acetaldehyde, 0.5 Gm.; sodium lactate, 0.6 Gm.; sodium pyruvinate, 1 Gm. Ergosterol was administered in doses of from 1 to 50 mg. per animal per day, the duration of the administration being from two to nineteen days. In the case of the other compounds, the period of administration varied from two to as long as 202 days. The number of animals in each series in which arteriosclerosis was present at the end of the experiments was as follows: formaldehyde bisulphide, 11 of 24; acetaldehyde, 11 of 25; sodium lactate, 5 of 19; sodium pyruvinate, 4 of 24; irradiated ergosterol, 16 of 26. With the aldehydes the degree of aortic involvement was greatest in from one to two weeks; after this period the animals appeared to become accustomed to the substances and the aortic lesions tended to heal. When irradiated ergosterol was used calcification and aneurysmal dilatation of the aorta were strikingly greater than after the other substances, and the degree of involvement was proportional to the duration of administration. In four dogs, each fed 9 Gm. of sodium lactate daily in a diet low in protein, over periods of from three to seven months, the results were negative, with the exception of one animal which revealed a slight degree of aortic change.

O. T. SCHULTZ.

EXPERIMENTAL RICKETS. T. SKAAR and K. HAEUPL, Virchows Arch. f. path. Anat. **271**:100, 1929.

Young dogs were fed on Mellanby's ricket diet. After three weeks the first signs of rickets appeared. The dogs were sick, awkward in their movements, ate

little, did not gain in weight. Roentgenograms of the radius and tibia showed poor ossification, thickening of epiphyses, widening of epiphyseal lines and frayed surfaces of the joints. Addition of 40 cc. of cod liver oil daily effected a rapid cure; the bone thickenings disappeared but the curvatures persisted. The phosphorus and calcium metabolism of the rachitic dogs was negative. The phosphorus and calcium content was low. After giving cod liver oil, the serum phosphorus rose quicker than the serum calcium. The bone of the cured animal contained less phosphorus and calcium than that of the control animal (which had 10 cc. of cod liver oil daily). In some dogs the phosphorus metabolism was more damaged, in others the calcium metabolism; there seem to be different forms of rickets. Large doses of phosphorus and calcium led to increase of phosphorus and calcium in the serum; but the bones of these dogs did not contain more phosphorus or calcium than those of the controls.

Nonlamellated bone was found in the controls also; it has nothing to do with rickets. Excessive formation of lime-free bone in the whole skeleton is characteristic of rickets. (N. Bocks method was used for demonstrating the lime-free bone.) The lime-free layers were ten times thicker than in the controls. Periosteal deposits of bone were less marked than in human rickets, but much more intense than in the controls. They are not of primary importance in the diagnosis of experimental rickets. Osteoblasts and osteoclasts did not differ from those in the controls and no such differences exist in human rickets. There were no signs of halisteresis. The bone-marrow of the rachitic dogs was fibrous; this is a secondary process due to irritation and stasis. The proliferating cartilage ("Knorpelwucherungszone") was from four to five times thicker than in the controls, occasionally from seven to ten times. The proliferating cartilage was vascularized from the marrow and from the perichondrium. The pathologic proliferations of the cartilage in the joint are secondary. It is the same with the formation of giant cells in hemorrhagic foci. The authors conclude that true rickets can be produced by deficient diet and cured by cod liver oil.

ALFRED PLAUT.

OXYGEN CONSUMPTION DURING MUSCULAR WORK IN HYPERTHYROIDISM AND IN HYPERTHYROID-LIKE STATES. H. HERXHEIMER, R. KOST and K. LANGE, Ztschr. f. klin. Med. **110**:1, 27 and 37, 1929.

The authors studied the consumption of oxygen during muscular work done by three groups of patients as compared with that of normal persons. Previous similar investigations on hyperthyroidism are criticized because of the paucity of observations made and because of the kind of work performed. The latter should be of a kind with which the subject is familiar and which requires no training to develop the necessary coordination. The work chosen in the present investigation was stair climbing done by each subject in slow, moderately rapid and rapid tempo. The Douglas bag method with gas analysis was used, samples of air being withdrawn for analysis immediately before and after the work done and at five minute intervals until a uniform level was reached. The increased consumption of oxygen due to work was compared with the recovery level rather than with the basal rate. The subjects studied, other than normal controls, were divided into three groups; eleven patients with instability of the sympathetic system or autonomic imbalance, with tachycardia and vasomotor instability, but with only slight subjective disturbance and with normal basal metabolic rate; a second group of twelve patients said to have exophthalmic goiter, with objective and subjective symptoms like those of hyperthyroidism but with no increase in basal metabolic rate, and eleven with hyperthyroidism accompanied by increased basal metabolic rate. In the first two groups the increased consumption of oxygen brought about by the work done was no greater than in the case of normal controls. The true cases of hyperthyroidism fell into three subgroups: in the first, there was no deviation in the consumption of oxygen as compared with normal; in the second, there was increased consumption and delay in recovery only when the work was done at rapid tempo; the third showed increased consumption of oxygen

and delayed recovery at all speeds of work. The last subgroup comprised persons with clinically the most severe forms of hyperthyroidism. The increased consumption of oxygen in the hyperthyroid group bore no relation to the degree of elevation of the basal metabolic rate.

O. T. SCHULTZ.

INSENSIBLE PERSPIRATION IN DECOMPENSATED CARDIAC DISEASE. E. ZAK, Ztschr. f. klin. Med. **110**:44, 1929.

Rubner first pointed out the importance in normal metabolism of the water lost by the body as insensible perspiration, and Benedict has recently made the determination of such loss practicable and has shown the amount of insensible perspiration to have a direct relation to the total energy metabolism, and within rather wide limits to be uninfluenced by clothing, temperature or air movement. Zak determined the insensible perspiration in three cases of decompensated cardiac disease, two of syphilitic aortitis with aortic regurgitation, and one of mitral stenosis with mitral and tricuspid insufficiency. In all, edema was constantly or intermittently present. In all, the water lost as insensible perspiration was greatly decreased. Even when the urinary output was increased above the water intake by digitalis or other therapy, the insensible perspiration still remained below normal. Increased oxygen intake with increased formation of water of oxidation within the tissues is not considered the true explanation of the interesting phenomenon noted. More probable but not yet proved the author considers a pathologically increased hydration of tissue colloids, the water being more firmly bound than normal, or increased intake of water from the atmosphere by the lungs and possibly also the skin, a condition which would interfere with the normal output of water from these sources.

O. T. SCHULTZ.

THE EFFECT OF ARSENIC ON THE MATURATION OF RED BLOOD CELLS. RAPHAEL ISAACS, Folia haemat. **37**:389, 1928.

The rate of growth and the factors influencing it, leading now to a precocious, now to a retarded maturation, is a problem which interests biologist and physician alike, for it involves cellular metabolism, that is, its growth and also probably the control of neoplastic tissues. For that purpose Isaacs used the erythrocyte which, he thinks, has certain advantages over other cells, in that it is easily available and recognizable; it has four distinct morphologic stages, and what is of great importance, the period of its maturation is short facilitating, thereby observations of changes at frequent intervals.

In previous studies the effect of hemorrhage, transfusion and roentgen irradiation on the maturation process has been investigated by the author. This work concerns itself with effects of arsenic on the maturation of the red blood corpuscles of the normal white mouse and also of some mice having tumors. Nontoxic and toxic doses of arsenic, acid and arsenious acid were used in the experiments. It was noted that nonlethal doses of arsenic caused a decrease in the percentage of both stages of young red blood cells, apparently as long as the arsenic was present in sufficient concentration in the body. After this, if no more arsenic was given there was a tendency for the more immature red blood cells to increase in percentage. In acute poisoning with arsenic, with death within twenty-four hours, there was no characteristic marked change in the absolute or relative number of young red blood cells.

In the tumor-bearing mice the depression in the number of young red blood cells was not so marked, but in these mice a study of the red blood cell formation showed that the bone-marrow did not have as much "reserve" as in the normal mice and that more cells were in the younger stages. The effect of arsenic acid is similar to that of arsenious acid in depressing the delivery of red blood cells from the bone-marrow, but the action is less intense and somewhat delayed.

Isaacs concludes that the arsenic solutions act as "depressors" of the bone-marrow with a decrease of production of young red blood cells. With the elimina-

tion of the arsenic the bone-marrow responds once more with an increase in the rate of maturation of the erythroblastic tissue and an increased production of young red blood cells.

B. M. FRIED.

THE LYMPHOCYTES IN NORMAL HUMAN BLOOD. AXEL WALLGREN, Arb. a. d. Pathol. Inst. d. Univ. Helsingfors **5**:317, 1928.

The technical details must be studied in the original article. In addition to physical permeability a "physiologic permeability" is postulated and ascribed to a distinct mechanism under the control of the vital action of the cell.

Pathologic Anatomy

THE RENAL LESIONS IN BRIGHT'S DISEASE. T. ADDIS, Am. J. M. Sc. **176**: 617, 1928.

By a study of the urine, patients with chronic interstitial nephritis may be divided into three groups to which the names arteriosclerotic, degenerative and hemorrhagic chronic interstitial nephritis have been provisionally attached. In the seventy-five instances in which the urinary observations were compared with the renal lesion as it existed at the time of death, the arteriosclerotic group was characterized by an arteriosclerosis of the renal arteries and by a patchy fibrosis of the cortex; the degenerative cases showed granular, fatty or necrotic changes in the tubule cells, while the hemorrhagic group was distinguished by the presence of inflammatory lesions in the glomeruli. There is evidence to justify the belief that, clinically, bleeding means an active glomerular inflammation, an increase of epithelial cells in the urine means tubular degeneration, and a continuing slight excess over the normal of casts, protein and cells in the urine probably means a renal arteriosclerosis.

PEARL ZEEK.

RAYNAUD'S DISEASE ASSOCIATED WITH CANCER OF THE STOMACH. T. IZOD BENNETT and E. P. POULTON, Am. J. M. Sc. **176**:654, 1928.

A case of Raynaud's disease with symmetrical gangrene of the fingers of both hands is reported. Postmortem examination revealed carcinoma of the stomach with metastasis to the inferior cervical ganglion. The presence of carcinoma cells in the ganglion was considered to be the cause of the Raynaud's disease. A similar case is quoted from the literature.

PEARL ZEEK.

SPONTANEOUS NONTUBERCULOUS PNEUMOTHORAX IN INFANCY AND CHILDHOOD. E. GORDON STOLOFF, Am. J. M. Sc. **176**:657, 1928.

The common causes of spontaneous pneumothorax in order of frequency are tuberculosis, pneumonia, emphysema and gangrene. A review of the literature since 1844 reveals eighty-four cases of nontuberculous origin. Pathogenetically, pneumothorax may be caused by (*a*) degeneration of the lung (abscess, gangrene, bronchiectasis, infarction and empyema) or (*b*) rupture of the lung due to congenital defect, emphysema or foreign body. Three cases of postpneumonic pneumothorax (nontuberculous) are described. The diagnosis was made by roentgenography.

PEARL ZEEK.

ACCESSORY SPLEENS. MAURICE MORRISON, MAX LEDERER and W. Z. FRADKIN, Am. J. M. Sc. **176**:672, 1928.

The failure of splenectomy to effect a permanent cure in essential thrombocytopenic purpura hemorrhagica may be caused by the presence of accessory

spleens which may undergo compensatory hypertrophy and gradually assume the pathic functions of the primary spleen. Four cases of thrombocytopenia are described, two with and two without accessory spleens.

PEARL ZEEK.

GASTRIC POLYPOSIS. ALFRED A. STRAUSS, JACOB MEYER and ARTHUR BLOOM, Am. J. M. Sc. **176**:681, 1928.

Two cases are added to the five previously reported in the literature. The differential diagnosis and treatment are discussed, and detailed microscopic and gross observations are given (with illustrations).

PEARL ZEEK.

A CASE OF EXTENSIVE BILATERAL PROGRESSIVE THROMBOSIS OF THE SMALLER BRANCHES OF THE PULMONARY ARTERIES. CHANNING FROTHINGHAM, Am. J. Path. **5**:11, 1929.

During life this patient clinically presented symptoms of unexplained shortness of breath and cyanosis on exertion gradually increasing over a period of months. The cause for it became apparent at autopsy as due to thrombosis of the smaller branches of the pulmonary arteries with resulting infarctions and injury to lung tissue. The thrombosis began in the smallest branches of the pulmonary arteries and propagated centripetally toward the larger branches. The cause for the beginning of the thrombosis or its tendency to propagate was not apparent. In the walls of some of the smallest branches of the pulmonary arteries were slight acute lesions for which the cause was not apparent. The relation of the tubercle-like lesions in the lung to the vascular lesions is unsettled.

AUTHOR'S SUMMARY.

A CASE OF MAMMARY GLAND TISSUE IN THE AXILLA. JOSEPH MCFARLAND, Am. J. Path. **5**:23, 1929.

The clinical history of the case, the surgical discovery of a collection of milk at the time of the operative removal of the tissue and the histologic observations all point clearly to this case as one of mammary tissue in the axilla in a woman, a unipara, 23 years of age.

AUTHOR'S SUMMARY.

THE INTIMAL LESION OF THE AORTA IN RHEUMATIC INFECTIONS. DAVID PERLA and MAX DEUTCH, Am. J. Path. **5**:45, 1929.

Two instances of macroscopic involvement of the aorta in recurrent rheumatic fever are described. A striking feature, which we believe has not been previously described, is the presence in one of the cases of an acute fibrinous lesion of the intima. In brief, the characteristics of the lesion are: Aschoff bodies in the adventitia; perivascular (in the acute stage, fanlike) infiltrations in the outer third of the media, with destruction of elastic tissue and muscle elements, and recent and organized fibrinous plaques in the intima, the connective tissue cells comprising the vascular organization tissue having a characteristic vertical orientation at the base of the intimal lesions.

AUTHORS' SUMMARY.

TISSUE CHANGES ASSOCIATED WITH VITAMIN "A" DEFICIENCY IN THE RAT. M. DAWSON TYSON and ARTHUR H. SMITH, Am. J. Path. **5**:57, 1929.

The principal changes associated with vitamin A deficiency in rats are a metaplasia of cuboidal or columnar epithelium in certain parts of the body, epithelial hyperplasia in various structures and infection. The metaplastic changes involve the following structures in order: the sublingual glands, the submaxillary glands, the epithelium of the renal pelvis and of the trachea and bronchi. The tongue is regularly involved before xerophthalmia appears. The serous type of sublingual gland is the first to be affected. The lesion in the tongue and submaxillary gland begins with a dilatation of the ducts and a metaplasia of the lining

epithelium accompanied by infection. In late cases the glandular tissue may be entirely destroyed by pressure from the dilated ducts and by necrosis due to infection. The submaxillary gland is not involved as constantly as the tongue. The epithelium of the renal pelvis may be involved fairly early. Metaplasia and infection are always present in the advanced cases. Renal calculi are prone to occur and when obstruction to the urinary outflow is present, pyonephrosis develops which is sometimes followed by perinephritic abscess. Epithelial metaplasia of the trachea and bronchi is not common. The most usual observation is an atrophy of the lining cells. Epithelial hyperplasia is striking in the tongue and renal pelvis. In the latter the hyperplasia overshadows the keratinizing process. Infection is always present even in the earliest stages and in late cases dominates the picture. No metaplastic activity has been seen without an accompanying infection, but infection has been observed in parts where metaplasia is absent. If the results of the dietary deficiency are not too severe, xerophthalmia clears rapidly with the administration of cod liver oil, and the weight curve rises abruptly. The extent of healing in the various organs depends largely on the amount of destruction due to infection which is present. Following the administration of cod liver oil abnormal epithelium and chronic or acute infection persist in the tongue and renal pelvis when the rat is apparently healthy.

AUTHORS' SUMMARY.

COMPENSATORY HYPERTROPHY OF THE THYROID. L. LOEB, Am. J. Path. **5**: 71 and 79, 1929.

Anterior pituitary substance, thyroid substance and thyroxin prevent compensatory hypertrophy of the thyroid in the guinea-pig and tend to produce changes in the thyroid that indicate a resting condition. The administration of potassium iodide does not prevent hypertrophy of the thyroid; on the contrary, the hypertrophy may be higher in animals receiving the iodide than in the control animals.

THE EFFECT OF UNDERFEEDING AND OF POTASSIUM IODIDE ON THE THYROID GLAND IN THE GUINEA PIG. JACOB RABINOVITCH, Am. J. Path. **5**:87 and 91, 1929.

Underfed guinea-pigs that have lost from 20 to 32 per cent of their weight show an entire absence of mitoses in the acinar epithelium of the thyroid gland, the colloid of which becomes solid and the acini small. The intraperitoneal injection of potassium iodide causes a rapid increase in the proliferation in the epithelium of the thyroid.

PRIMARY HYPERNEPHROMA OF THE LIVER. I. ABELL, Ann. Surg. **87**:829, 1928.

This is a report of a case of hypernephroma of the liver in a child 13 months of age, and a summary of ten cases collected from the literature.

N. ENZER.

BENIGN TUMORS OF THE STOMACH. J. T. MASON and M. F. DWYER, Ann. Surg. **88**:866, 1928.

Three cases are reported of leiomyoma, polyp and fibromyoma of the stomach. None of these cases gave any symptoms, and the lesion was demonstrated by the roentgen ray. In one case the condition had been diagnosed as spindle cell sarcoma, but after seven years the patient was still alive and the pathologist reclassified the case as a leiomyoma.

N. ENZER.

PRIMARY EXTRA-RENAL HYPERNEPHROMA. A. E. BOTHE, Ann. Surg. **89**:1028, 1928.

The author reports a case of a tumor in the region of the right suprarenal gland with metastases in the liver, but not involving either the kidney or the suprarenal gland. The tumor had the histologic structure of hypernephroma.

N. ENZER.

FOCAL NECROSIS OF THE LIVER. J. W. EDINGTON, J. Path. & Bact. **32**:1, 1929.

The primary lesion in focal necrosis of the liver in infection with *B. aertrycke* is death of liver cells; the infiltration with macrophages is secondary. Bile stasis is an important factor in localizing the lesions.

AUTHOR'S SUMMARY.

CHRONIC PEPTIC ULCER OF THE OESOPHAGUS. M. J. STEWART and S. J. HARTFALL, J. Path. & Bact. **32**:9, 1929.

A case of chronic peptic ulcer of the lower end of the esophagus is reported. The chief symptoms were high epigastric pain of five months' duration and recurrent hematemesis for a fortnight; dysphagia was not a prominent symptom. Death was due to perforation of the ulcer into the right pleural sac. An interesting feature of the case was the presence in the upper part of the esophagus of two large patches of heterotopic gastric mucous membrane of fundal type; the possible relationship of this developmental abnormality to chronic peptic ulceration of the esophagus is discussed.

AUTHORS' SUMMARY.

RETROPERITONEAL GANGLIONIC NEUROMA. D. F. CAPPELL, J. Path. & Bact. **32**:43, 1929.

A case is recorded of an unusually large ganglionic neuroma which presents throughout a uniform structure of adult ganglionic cells and nerve fibers. The majority of the fibers are of nonmedullated type and the remarkable feature is their enormous number. They possess a well formed sheath of Schwann and an outer connective tissue sheath of Henle. Two varieties of axis cylinder processes have been recognized; coarse relatively uniform fibers, and fine fibers with the varicosities of sympathetic type. The interstitial tissue is unusually myxomatous, but no neuroglial elements other than the neurilemma cells have been recognized. No trace of rosets or other neuroblastic elements has been found, and the subsequent history of the case confirms the view that the tumor is of simple type.

AUTHOR'S SUMMARY.

THE NERVOUS SYSTEM IN RATS FED ON DIETS DEFICIENT IN VITAMINS B_1 AND B_2. RUBY O. STERN and G. MARSHALL FINDLAY, J. Path. & Bact. **32**:63, 1929.

Rats fed on a diet deficient in both vitamin B_1 and B_2 exhibit only slight chromatolytic changes in the ganglion cells of the cord. Rats fed on a diet deficient in vitamin B_1 exhibit the same changes but to a greater extent for the same duration of life. In addition, when symptoms of paralysis are of long standing, early degeneration may be found in the myelin of the peripheral nerves. The histologic changes found in the nervous system of rats fed on a diet lacking vitamin B_2 consist in swelling and vacuolation of the anterior horn cells of the spinal cord with the deposition in them of lipochrome pigment, a noticeable increase in the surrounding satellite cells and an increase in the number of granules in the peripheral nerves.

AUTHORS' SUMMARY.

A CASE OF DIABETES MELLITUS WITH ACROMEGALY AND LIPAEMIA. JOHN GRAY, J. Path. & Bact. **32**:71, 1929.

In a patient dying from diabetic coma and presenting also certain features of acromegaly, the following lesions were noted post mortem: lipemia, consequent mononuclear hyperplasia in the spleen, pancreatic, hepatic and renal cirrhosis, cholelithiasis, chromophobe adenoma of the pituitary gland, gastric catarrh with multiple gastric ulcers and hemorrhage into the stomach.

AUTHOR'S SUMMARY.

DIFFUSE AND NODULAR FIBROSIS OF ADVENTITIA OF AORTA. W. G. BARNARD, J. Path. & Bact. **32**:95, 1929.

A widespread fibrosis of the adventitia of the aorta is described; the suggestion is made that it is due to rheumatism.

AUTHOR'S SUMMARY.

SIDEROSIS OF THE GLOBUS PALLIDUS: ITS RELATION TO BILATERAL NECROSIS. GOEFFREY HADFIELD, J. Path. & Bact. **32**:135, 1929.

The walls of the blood vessels of the healthy globus pallidus are often infiltrated with iron salts which are derived from the nucleus itself. It is likely that the process is one of evolutionary atrophy. It predisposes to the acute bilateral destruction of these nuclei which is frequent in coal-gas poisoning.

AUTHOR'S SUMMARY.

CONGENITAL VALVES, PSEUDOVALVES AND STENOSIS OF THE PYLORUS AND DUODENUM. A. COSTA, Arch. di pat. e clin. med. **7**:501, 1928.

At the autopsy of a woman, aged 60, a valvelike formation was found in the pyloric canal; the basal attachment of this pyloric valve measured 2 cm. in width, 1 cm. in length and 3 mm. in thickness. In its close vicinity, there was another but smaller, tonguelike, mucous projection. Microscopically, it showed the structure of a normal mucosa (transition between pyloric and duodenal type) and contained a few smooth muscle cells, which were branching from the muscularis mucosae. The author classified this valvular formation of the pylorus, which was observed only once in about 20,000 autopsies, as a developmental disturbance and as an excess in growth. The literature contains only one paper dealing with this subject, published by Arregger in 1896. These congenital valves of the pylorus should not be confused with pseudovalvular formations, which are the result of a benign neoplasm, as described by Magnus-Asleben, and originate from a proliferation of glandular and muscular tissues (adenomyoma of the pylorus). The author then describes a typical case of a pyloric pseudovalve due to traction, microscopically an adenoma, in a man 67 years of age. Various forms of congenital pyloric stenosis are discussed in detail and, in accordance with Chiari, three types are introduced: (*a*) congenital stenosis of mucous type (stenosis of Landerer-Maier type); (*b*) congenital stenosis of muscular type (hypertrophic stenosis, stenosis of Hirschsprung type), and (*c*) congenital stenosis of combined type (a variety of Landerer-Maier type). The theories regarding the development of congenital stenosis of the duodenum and of the duodenal atresia are exhaustively presented. The studies of Schridde, Beneke and Tandler, which tend to prove an embryonal epithelial occlusion of the duodenum, are contrasted with the theories propagated by Marchand, Thorel and Fanconi, who assume the existence of a fetal enteritis.

E. L. MILOSLAVICH.

THE RETICULAR TISSUE IN AMYLOID DEGENERATION. L. LA GRUTTA, Sperimentale: Arch. di biol. **82**:381, 1928.

The changes in the reticulum in organs of man or in the organs of animals, in which amyloid degeneration is not far advanced, are increase of volume, varicosity, disintegration and resistance to impregnation of the fibrils by silver. The appearances suggest that the reticulum is concerned in the early formation of amyloid.

FUNGI IN GASTRIC ULCERS. O. BARTOLI, Sperimentale: Arch. di biol. **82**:421, 1928.

Fungi are frequently found in gastric ulcers, not only in the superficial layers and necrotic areas, but also in the deeper parts. The fungi, while perhaps not the cause of the ulcer, may be important factors in its maintenance and in changing an acute into a chronic ulcer.

MEDIAN CERVICAL CYST AND FISTULA. A. MAGLIULO, Sperimentale: Arch. di biol. **82**:455, 1928.

The most frequent congenital median malformation of the neck is thyroglossal cyst, arising from remnants of the thyroglossal duct. Median cervical cysts may arise also from displaced thyroidal tissue. These cysts may result in median fistula.

PRIMARY, GENERALIZED ROUND CELL SARCOMA OF THE LYMPH GLANDS. E. HERZOG, Centralbl. f. allg. Pathol. u. path. Anat. **44**:129, 1928.

A girl, aged 15, entered the hospital because of painless, generalized enlargement of the lymph glands of five weeks' duration. Two weeks later a small tumor developed beneath the skin of the right third intercostal space, and eight days later an abscess of the palate. The lymph glands were the size of a plum; the Wassermann reaction of the blood was negative, and the blood picture was typical of a secondary anemia. A clinical diagnosis was made of aleukemic leukemia. At autopsy there was a tumor-like systemic involvement of all lymph glands, and there were small metastases in the pericardium, trachea, sternum, skin of the right shoulder and marrow of the femur. Microscopically, the structure of the lymph glands was distorted by many large round or polygonal cells with abundant protoplasm with large vesicular nuclei rich in chromatin and with abundant mitoses. The capsules of the lymph glands generally were thickened but free from infiltrations of tumor cells or small lymphocytes, whereas in the region of the mediastinum and trachea the invasive character of the tumor was evident. The origin of this large round cell sarcoma of the lymph glands was therefore thought probable in the mediastinum.

GEORGE RUKSTINAT.

DIFFUSE ACUTE INTERSTITIAL ADENOHYPOPHYSITIS. W. BERBLINGER, Centralbl. f. allg. Pathol. u. path Anat. **44**:161, 1928.

In a woman, aged 34, who was eight months' pregnant, with a blood pressure of 180 systolic and 140 diastolic, scanty urine containing 20 per cent albumin and a premature separation of the placenta necessitating delivery, death occurred from uremia. The hypophysis weighed 0.86 Gm. and its posterior lobe was normal. In the anterior lobe, particularly in its dorsal portion, there were infiltrations of lymphocytes and lymphoblasts, and rarely leukocytes about the alveoli and along the capillaries. The capillary endothelium was unchanged. The alterations herein noted were found lacking in the hypophyses of five other women dying of eclampsia.

GEORGE RUKSTINAT.

THE HARDNESS OF GLANDULAR ORGANS AND THE CHANGES AFTER DEATH. HANS MELTZER, Klin. Wchnschr. **7**:2477, 1928.

Sclerometric measurements of the liver, spleen and kidney in a variety of warm-blooded animals were made at and following death for several days. There is a definite increase in the hardness of these tissues (regularly of the liver and kidney, not without exception of the spleen) which reaches its maximum from three to eight hours after death. This change, in theoretical discussion, is ascribed to a postmortem alteration of the protein colloid of the cells.

AUTHOR'S SUMMARY.

SUPPURATION OF THE THORACIC DUCT. E. KRYLOFF, Virchows Arch. f. path. Anat. **266**:1, 1927.

An instance of this rare condition is described, which occurred during an attack of grip.

B. R. LOVETT.

THE EFFECT OF STRETCHING ON SKELETAL MUSCLE. A. STAUSS, Virchows Arch. f. path. Anat. **266**:4, 1927.

During pregnancy, destruction and new formation of muscle fibers in the embryonic manner were observed. In cases of infection, especially acute, more varied and marked degenerative changes were found. During great increase in the intra-abdominal pressure, tearing and scar formation occurred. Proliferation of nuclei at the ends of the fibers indicated an appositional growth of the stretched abdominal muscle, which should be a suitable object for investigations of the growth and hyperplasia of the musculature in general.

B. R. LOVETT.

BONE FORMATION IN THE WALL OF THE HEART. H. EDELMANN, Virchows Arch. f. path. Anat. **266**:51, 1927.

Twenty-three instances of bone formation in the heart muscle have been described in the literature, only one of which was in man. In this case a piece of long bone with a cartilaginous epiphysis was found in the left auricular wall of a guinea-pig. The author explains the development of this anomaly according to the blastomere theory of Marchand and Bonnet, rather than as a metaplastic growth.

B. R. LOVETT.

CONSEQUENCES OF LIGATION OF THE HEPATIC ARTERY. L. LOEFFLER, Virchows Arch. f. path. Anat. **266**:55, 1927.

Loeffler studied the effects of ligation of the hepatic artery in sixty rabbits. General changes of a mild nature occurred in the portal areas: widening of the lymph vessels, the branches of the portal vein and the bile ducts, and later increase in collagenic fibers without cell increase, and decrease in elastic and muscle tissue in the vessel walls. He attributed these changes, not directly to deprivation of blood supply, but to paralysis of the vessel walls, since nervous tissue is the first to suffer from anemia. In the lobules of the liver themselves, partially deprived of blood supply, hyperemia occurred: widening of the capillaries with slowing of the blood flow, and shrinking of the liver cells. Nerve injury was regarded as the basis for this change also.

Localized changes, less constant but of more marked degree, were also found. Necrosis of the gallbladder was almost constant, followed by leakage of bile into the parenchyma immediately around it, so that it too became necrotic. Scattered sections of the larger bile ducts underwent necrosis in from thirty to 120 minutes. Paralysis and dilatation of the walls took place, allowing them to become permeated with bile, which acts as a strong chemical irritant to the nervous mechanism. This change in the ducts was sometimes accompanied by extensive stasis and necrosis in the neighboring lobules, also attributed to the irritant effect of the bile. The larger necrotic places became surrounded by a zone of fibrous tissue, with hypertrophied bile ducts and atrophied parenchyma.

Ligation of the hepatic artery was shown to act, therefore, not directly, but through the irritant effect of the bile set free into the tissue. The change reached its height during the first few days, and thereafter was regressive. The liver ceased to function in glycogen and fat metabolism for a time. Deaths were in proportion to the number and extent of the necrotic places.

B. R. LOVETT.

THE EFFECT OF ACID AND ALKALINE FEEDINGS PRODUCING AMYLOID IN MICE. R. RABL, Virchows Arch. f. path. Anat. **266**:133, 1927.

In mice fed on a diet rich in cholesterol, and either acid or alternating acid and alkaline in reaction, the presence of amyloid could be shown in a number of organs. It was most frequent in the spleen and liver, less so in the duodenum, kidneys and pancreas. Skin infections could not be ruled out in all cases. These feedings were also frequently accompanied by waxy degeneration in the heart and body musculature, and calcification of the arteries. Mice fed on alkaline

foods tended to develop anemia, but rarely showed amyloid or waxy degenerations. In the production of this form of degeneration, therefore, acid foods and those rich in cholesterol seem to be of significance.

B. R. LOVETT.

CHANGES IN THE SKELETAL MUSCULATURE IN TRICHINOSIS. H. NEVINNY, Virchows Arch. f. path. Anat. **266**:185, 1927.

Five cases of trichinosis in man and eighteen experimental infections in animals were studied. Gross anatomic changes in the muscles were found in only two animals and in none of the cases in man. The presence of glycogen in *Trichinellae* could be easily demonstrated, while the surrounding muscle was poor in this substance. The fibrillar substance showed degeneration, with fine, basophilic granulation, besides waxy and hydropic degeneration, and simple atrophy. Fatty change was marked in three cases in human beings, but was insignificant in the animals. Two stages in encapsulation were distinguishable. First, the coiled worms were seen to be surrounded by a substance made up of the basophilic, granular contents of the fibers. In the chronic stage, permanent hyaline capsules were formed. This process was explained as an antigen-antibody reaction. Foreign body giant cells, of mesenchymal origin, were observed near the dying *Trichinellae*. Clinically observed painfulness corresponded to the degree of exudate and cellular infiltration in the muscles. This inflammatory reaction was more marked in man than in the animals. Nonencapsulated worms rapidly underwent destruction, in which process collections of white blood cells and tissue cells played a part. Destruction with liberation of the substance of *Trichinellae* was especially prominent in man, accounting for the severe general symptoms of the disease. The observations indicated that man reacts more strongly to *Trichinellae* than do guinea-pigs or rabbits, while rats readily succumb to acute intestinal trichinosis.

B. R. LOVETT.

A RARE MALFORMATION OF THE TRICUSPID VALVE. A. ARNSTEIN, Virchows Arch. f. path. Anat. **266**:247, 1927.

A case of congenital malformation of the tricuspid valve (Ebstein's disease) is described. There was dilatation of the right auricle, contraction of the right ventricle with poor development of its wall, and open foramen ovale. Clinically, systolic and diastolic murmurs, thrills, cyanosis and polycythemia were observed.

B. R. LOVETT.

HISTOLOGIC FINDINGS IN THE RETICULO-ENDOTHELIAL SYSTEM IN DIFFERENT FORMS OF PUERPERAL FEVER. H. E. SCHEYER, Virchows Arch. f. path. Anat. **266**:255, 1927.

The course of puerperal fever is influenced, aside from the virulence of the organism, by the resistance of the body, especially the reactivity of the reticulo-endothelial system. Three types of the latter have been described: lack of reaction, good reaction and reaction at first satisfactory but becoming exhausted. In patients with different forms of puerperal fever, lack of reaction was found in those dying of foudroyant sepsis and rapidly fatal peritonitis. Reaction at first active, but becoming exhausted, was correlated with thrombophlebitis ending fatally after a prolonged course. In patients who recovered, satisfactory reaction of the reticulo-endothelial system could be assumed in the absence of occasion for histologic examination.

B. R. LOVETT.

LYMPHOSTASIS. W. TALALAIEV, Virchows Arch. f. path. Anat. **266**:268, 1927.

Following interruption of lymph flow, growth of the epithelium and stroma occludes the lumen of the vessel. In the nodes, the adenoid tissue disappears first, the reaction centers remain somewhat longer, the sinuses are converted into a network of lymph capillaries and the stroma becomes collagenous.

B. R. LOVETT.

EPITHELIAL METAPLASIA IN THE LUNGS. P. GUNKEL, Virchows Arch. f. path. Anat. **266**:310, 1927.

An instance of metaplasia on the basis of a chronic inflammation is described, in which cylindric and pavement epithelia were observed in the alveoli of the lungs.

B. R. LOVETT.

A LYMPHO-EPITHELIAL TUMOR OF THE THYROID. A. BABES, Virchows Arch. f. path. Anat. **266**:320, 1927.

A benign tumor of the thyroid is described, probably originating from thymus tissue. It consisted of lobules of lymphoid cells, containing islands and strands of epithelium.

B. R. LOVETT.

CHANGES IN THE THYROID GLAND IN AVITAMINOSIS B. S. A. SATWORNITZKAJA and W. S. SIMNITZKY, Virchows Arch. f. path. Anat. **266**:329, 1927.

In the thyroids of rats on a diet lacking in vitamin B, there was found at first increased secretory activity, with hypertrophy and new growth of follicles and increase in colloid. Later, rupture of several follicles occurred, with escape of colloid, along with necrobiosis of the follicle cells. Since no repair took place, this process was followed by decrease in the size of the gland. In the end-stage, signs of exhaustion and decreased function became evident, but not to any marked degree.

In the thyroids of pigeons the same changes were observed, except that evidence of terminal decrease in function was lacking. Necrobiotic changes in the single cells appeared to be the result of increased activity with disturbance in nutrition, in consequence of the vitamin lack. These changes were too slight, however, to account for a decrease in function.

The results present no evidence of significant decrease in secretion during vitamin B inadequacy, but, on the contrary, show an increase, for a certain length of time in rats, and until the end in pigeons.

B. R. LOVETT.

HERMAPHRODITISM. G. SCHAPIRO, Virchows Arch. f. path. Anat. **266**:392, 1927.

A hermaphrodite is described whose secondary sexual characters partook of both masculine and feminine types. One of the internal sex organs was an immature ovary, and the other a mixture of ovary and testis. Removal of these organs and inplantation of animal testes failed to change the patient in any way. The author discusses classifications of hermaphroditism, and finds a difference in degree only between the true and pseudo types.

B. R. LOVETT.

DISPLACEMENT OF THE POSTERIOR LOBE OF THE HYPOPHYSIS. A. PRIESEL, Virchows Arch. f. path. Anat. **266**:407, 1927.

Priesel observed several instances in which the posterior lobe of the hypophysis lay outside the sella on the base of the brain. It was connected with the anterior lobe by a thin strand of tissue. Three types of displacement have been found. There was no functional significance associated with this anomaly.

B. R. LOVETT.

SYMPATHETIC TUMOR OF THE SUPRARENAL GLAND. F. MATZDORFF, Virchows Arch. f. path. Anat. **266**:416, 1927.

A tumor of the suprarenal gland was examined at autopsy, consisting of cells of sympathetic nervous system origin. The liver tissue was almost entirely replaced by cells of the same type. This was thought to be a primary disease of the liver rather than a metastatic growth.

B. R. LOVETT.

THE APOCRINAL SWEAT GLANDS. H. HERZENBERG, Virchows Arch. f. path. Anat. **266**:422, 1927.

An investigation was made on 200 cadavers of men, women and children of these large sweat glands, found chiefly in the axillary and genital regions, and secreting a substance of characteristic odor. The full number of glands was found at birth, but actively could not be distinguished before sexual maturity. The number appeared to be somewhat greater in boys than in girls. In adults, the glands were equally widespread in the two sexes, and were functional from puberty throughout the rest of life, with some variations. Thus, in wasting disease and in old age their activity decreased along with that of other organs. In women, there was hypertrophy and hypersecretion during menstruation and pregnancy, and moderation of activity without complete cessation after the menopause. The glands appeared to function not only as "accessory sex glands," but also as organs for determining the characteristic odor through most of life, independently of the other sex organs.

B. R. LOVETT.

HISTOGENESIS OF RENAL TUBERCLES. CLAUSSEN, Virchows Arch. f. path. Anat. **266**:456, 1927.

The first changes in miliary renal tuberculosis of pigs and cows were localized in the interstitial tissue of the cortex, in the form of small collections of epithelioid and round cells. Primary disease of the glomeruli, as occurs in experimental infections, was never found. The cells making up the tubercle were derived from the histiocytes of the interstitial tissue and the endothelial cells of the capillaries, never from the renal epithelium. Fully developed tubercles showed the usual epithelioid and lymphoid zones, and later gave evidence of degeneration in the form of fatty change and finally caseation.

B. R. LOVETT.

TUBERCULOSIS OF THE SEROUS MEMBRANES. E. RANDERATH, Virchows Arch. f. path. Anat. **266**:475, 1927.

This histologic study of tuberculosis of serous membranes from autopsy material revealed the two forms, miliary tuberculosis without exudate and tuberculous inflammation with exudation, but the transition between the two was found to be gradual. The development of the exudate could be traced through various stages, beginning with injury to the surface epithelium, followed by circulatory disturbance and exudation. The exudate in this stage varied in composition and in the predominant cell type, and was not of a specific character except as it contained bacilli. The growth of granulation tissue followed rapidly, with the formation of characteristic tubercles, the first specific change. Caseation was observed in some of the cases, both in the granulation tissue and in the exudate, with masses of bacilli, and involving all the cells present in the region. Granulation tissue could sometimes be found growing into the caseous masses. In the end-stage, there was conversion of the organized exudate into solid, nonspecific scar tissue.

B. R. LOVETT.

TUBERCULOSIS OF THE PAROTID GLAND. L. HASLHOFER, Virchows Arch. f. path. Anat. **266**:499, 1927.

A case of isolated tuberculosis of the parotid gland is described, of the nodular caseous type, with miliary and conglomerate tubercles. The mode of infection is discussed, and of the various possibilities, infection through the blood or lymph stream is held to be the most probable.

B. R. LOVETT.

"YELLOW (CHROMAFFIN)" CELLS IN THE GASTRO-INTESTINAL TRACT. H. HAMPERL, Virchows Arch. f. path. Anat. **266**:509, 1927.

The yellow cells are one of the types found in the intestinal epithelium of man and most vertebrates. They can be distinguished by the staining reaction with

silver salts, which color the nuclei and granules black without the addition of reducing substances. This reaction distinguishes them from the chromaffin cells of the suprarenal gland, which they resemble somewhat. The granules are situated at the base of the cells, below the round nucleus. The yellow cells probably originate from undifferentiated cells of the intestinal epithelium, and have an excretory function about which little is known.

In the stomach, Hamperl found these cells in the islands of intestinal mucosa which appear there in the various conditions commonly known as "chronic gastritis." Yellow cells were absent or few in number in normal gastric mucous membrane, but were frequent in "chronic gastritis," with or without carcinoma. He regards them as the result of faulty cell differentiation in the course of regeneration of the epithelium. Yellow cells were found predominating in carcinoid tumors, but were numerous in only three of fifty-one other carcinomas of the gastro-intestinal tract, one in the cecum, one in the rectum and one in the stomach. Hamperl does not believe in a fundamental distinction between carcinoids and other intestinal carcinomas.

B. R. LOVETT.

THE ETIOLOGY OF GASTRIC AND DUODENAL ULCERS. I. HONDA, Virchows Arch. f. path. Anat. **266**:549, 1927.

Injections of lycopodium into the gastric and duodenal veins of dogs did not produce ulcers, but injection into the arteries was followed by the development of ulcers in more than 100 dogs. In the stomach, the location, most frequently at the pylorus and lesser curvature (regions poor in arterial anastomoses), and the form, round with steplike margins, resembled the round ulcer in man. The lycopodium produced thrombosis, chiefly in the arteries of the submucosa, followed by anemic necrosis of the epithelium, and digestion by the gastric juice. Thus, arterial circulatory disturbance appeared to be the cause of the ulcer. Erosions also were sometimes produced, but these healed promptly, and bore no relation to the ulcers. The latter healed within one month. For production of a chronic lesion, some other disturbing factor was needed, such as passive congestion through ligation of the gastric veins, removal of the celiac ganglion and plexus, or injection of *Staphylococcus aureus*. In the chronic ulcers, the characteristic form, as well as evidence of arterial thrombosis, became indistinct in the course of time. This fact makes it understandable that organic changes in the arteries of the region of the ulcer become difficult to recognize. Results were similar following injections into the duodenal arteries.

A study of autopsies on man revealed: ulcers present in 4.79 per cent, the most frequent age being the fourth decade, men affected oftener than women, and circulatory disturbance, atherosclerosis, arteritis obliterans and thrombosis frequent accompaniments. Honda believes that ulcers arise on the basis of organic change in the gastric arteries with digestion of the mucous membrane by gastric juice. The chronicity depends on factors influencing reparative activity, passive congestion, nervous disturbance and infection.

B. R. LOVETT.

ENDARTERITIS OBLITERANS. H. GOECKE, Virchows Arch. f. path. Anat. **266**:609, 1928.

Necropsy of a patient who died from endarteritis obliterans revealed changes in the medium-sized arteries of the extremities, consisting of growth of the intima and consequent narrowing or obliteration of the lumen. No evidence of a primary arteriosclerosis or thrombosis was found. The intimal growth was attributed to repeated spasm with subsequent dilatation of the vasa vasorum supplying the medium-sized arteries, leading to increased permeation of the vessel wall by fluid. Gangrene was attributed to alternating spasm and dilatation in the capillary region, along with slowing of the blood stream, so that a slight trauma was followed by complete stasis and necrosis. As etiologic factors, the action of nicotine, alcohol, cold and other injurious agents on constitutionally inferior nerves of the vascular system is suggested.

B. R. LOVETT.

THE STRUCTURE AND PHYSIOLOGIC CHANGES OF THE CEREBRAL ARTERIES. W. M. HACKEL, Virchows Arch. f. path. Anat. **266**:630, 1928.

Hackel points out the importance of recognizing the normal histologic structure and the changes due to the age of the cerebral arteries. His studies showed the chief characteristics of these arteries to be the thick lamina elastica interna, absent lamina elastica externa and poorly developed adventitia. Splitting of the lamina elastica interna was observed, beginning in childhood in the largest arteries, and spreading to the smaller vessels during later life. He concluded that hyperplasia of the elastic tissue of the intima, of greater or less degree, is a normal physiologic change of advancing age.

B. R. LOVETT.

THE SIGNIFICANCE OF THE VENAE MINIMAE THEBESII FOR THE BLOOD DISTRIBUTION TO THE HEART MUSCLE. J. KRETZ, Virchows Arch. f. path. Anat. **266**:647, 1928.

Kretz reached the following conclusions from perfusion experiments carried out on the hearts of cadavers: The Thebesian vessels are an important part of the coronary system. They are found in all sections of the heart, and are especially well developed in the interventricular septum and at the apex. They provide a direct connection between the coronary vessels and the chambers of the heart. Conditions for blood flow through the Thebesian vessels are most favorable during systole, while the coronary vessels carry most blood during diastole. The presence of the Thebesian vessels and the consequent possibility of nourishing the heart from its own chambers explain the frequent lack of correlation between disease changes in the coronary arteries and the function of the myocardium. In spite of high grade narrowing of the coronaries, the heart can still be capable of full work. A further possibility of nutrition lies in absorption of substances from the blood directly through the endocardium.

B. R. LOVETT.

RETICULOCYTES IN EMBRYOS AND THE NEW-BORN. R. JÜRGENS, Virchows Arch. f. path. Anat. **266**:676, 1928.

The blood of 300 mouse embryos was investigated. Two developmental series of red cells could be distinguished, the megaloblastic and the normoblastic. In young embryos, all erythroblastic cells contained vitally stained granulations, and a definite formation and growth of substantia granulofilamentosa could be determined, similar for both series. In later embryonic life, the number of reticulocytes diminished progressively with the disappearance of the cell nuclei until birth. New-born mice had an average of from 60 to 70 per cent of reticulocytes, falling to from 30 to 40 per cent in the first hours of life, and to from 0.5 to 2 per cent after a few weeks. In human infants the percentage was 7 at birth, 2 at 10 days and 0.7 at 6 weeks. In premature infants, the number was much greater, from 11 to 30 per cent at birth. The substantia granulofilamentosa represents a constant morphologic stage in the process of normal development of all hemoglobin containing blood cells in man and in animals. This substance is a remainder of the original blood cell protoplasm, and diminishes as pykinosis and karyolysis of the nucleus occur, until it disappears entirely in the mature cell.

B. R. LOVETT.

SIGNIFICANCE OF LIPOIDSIDEROSIS OF THE CEREBRAL CAPILLARIES FOR HYPERTONIA AND ARTERIOSCLEROSIS. M. MÜHLMANN, Virchows Arch. f. path. Anat. **266**:712, 1928.

The author states that essential hypertension is due to an obstruction to the circulation, the cause of which is unknown, but is generally assumed to be of a nervous nature. Physiologic hypertension with advancing age follows from the comparative narrowing of the arteries in comparison with the size of the heart. Pathologic hypertension is distinguished chiefly by its effect on the brain. The cerebral arteries are characterized by the presence of lipoid granules in the endo-

thelium, with increasing blood pressure. The course of these iron-containing granules is the red blood cells which are driven into the wall under the influence of high pressure, and are phagocytosed. From there they may be carried to the nerve cells; lipoidsiderosis of the brain. As a consequence of the narrowing of the arteries, with hypertension and oxygen insufficiency, the process becomes itself a cause of further hypertension, and is the beginning of arteriosclerosis. Pathologic hypertonia is then the result of the action of injurious agents (infection, intoxication) on the physiologic hypertension, which is due, first, to conditions of growth, and, second, to lipoidsiderosis of the cerebral capillaries. Arteriosclerosis is the end-result of hypertension.

B. R. LOVETT.

CEREBRAL CHANGES IN HUMAN TRICHINOSIS. E. GAMPER and G. B. GRUBER, Virchows Arch. f. path. Anat. **266**:731, 1928.

Although cerebral symptoms have long been known to occur in severe cases of trichinosis, there has been little investigation of the pathologic changes. The authors examined the brain of a person who died in the fifth week of an acute trichinosis, and found edema and infiltration of the markedly hyperemic meninges, along with regressive and progressive changes in the brain. The latter consisted of nodules of glia cells, in some of which *Trichinae* could be demonstrated. The regressive changes observed were scattered necrotic foci, sometimes accompanied by embolism or thrombosis of the vessels, fatty degeneration and growth of glia fibers. It seems justifiable, therefore, to speak of encephaltis in trichinosis.

B. R. LOVETT.

SPLENIC INFARCTS IN TYPHOID FEVER. S. BÉZI, Virchows Arch. f. path. Anat. **266**:748, 1928.

The circumscribed necroses in the spleen occurring in typhoid fever are infarcts, caused by necrosis and tearing of the lamella elastica interna and consequent thrombosis of the artery. Necrosis of the elastic tissue is due to the toxin of the typhoid bacilli. These infarcts are specific for typhoid infection, and can be distinguished from those arising from embolism. In more than 500 cases, 4.15 per cent showed infarcts arising from tearing of the elastic tissue, occurring most frequently during the fourth week. Suppuration of the infarcts is usually due to the typhoid bacillus itself. There is no relation between central necrosis of the mesenteric lymph nodes and the frequency of splenic infarcts.

B. R. LOVETT.

THE LIVER IN AFRICAN YELLOW FEVER. W. H. HOFFMANN, Virchows Arch. f. path. Anat. **266**:769, 1928.

Histologic examinations were made of the livers from a number of cases of suspected yellow fever in West Africa, and in all the presence of this disease could be demonstrated. The chief characteristic was the simultaneous presence of numerous cells which had undergone fatty degeneration and completely necrotic cells, mixed together. Near the central vein and at the periphery were a few well preserved cells, but the picture was never one of a purely central or peripheral necrosis. These constant changes were attributed to the toxin of *Leptospira icteroides*. The African cases showed full agreement with those in the American epidemics. Similar changes are found only in acute yellow atrophy and in a few intoxications, never in acute infectious diseases. Histologic examination of the liver is the simplest and most reliable method for showing the presence of yellow fever, and hence is of the greatest value in the prevention and checking of epidemics.

B. R. LOVETT.

THE ETIOLOGY OF MALACOPLAKIA OF THE BLADDER. Z. KAIRIS, Virchows Arch. f. path. Anat. **266**:788, 1928.

A case of malacoplakia of the urinary bladder is described in a girl, aged 1½ years, with an infected double kidney on one side. This disease is usually found

in older persons. Cystoscopic examination shows the mucous membrane studded with yellow-white, raised plaques, with a depression in the center, and sometimes ulceration in the later stages. Histologically, the plaques are made up of lymphocytes and large round or angular cells, with small round nuclei, corresponding to fibroblasts, which are characteristic for the condition. There may also be iron-containing inclusion bodies. The condition has been variously regarded as a granuloma, the result of nonspecific infection, or of long-standing cystitis. The latter seemed to be the causative factor in this case.

B. R. LOVETT.

LIPOMA OF THE ADIPOSUM PARARENALE. L. JAFFÉ, Virchows Arch. f. path. Anat. **266**:801, 1928.

Jaffé reports a case of lipofibrosarcoma, with necropsy observations, in which the tumor weighed 11.3 Kg. The condition originated in the body of fat behind and lateral to the kidneys. The tumor was bilateral, retroperitoneal on one side and intraperitoneal on the other. He found nine instances in the literature of tumors with a similar origin, some pure lipomas and some mixed with fibrous or myxomatous tissue.

B. R. LOVETT.

COMPLETE RUPTURE OF THE RIGHT BRONCHUS. S. I. KRINITZKI, Virchows Arch. f. path. Anat. **266**:815, 1928.

A girl, aged 10 years, suffered a severe injury when a heavy wine cask fell on her chest. Twenty-one years later, at autopsy, a complete rupture of the right main bronchus 3 cm. below the bifurcation was found. The right lung was completely atelectatic, and, while the left showed marked tuberculosis, the right was entirely free from involvement.

B. R. LOVETT.

THE FUNCTION OF LYMPHOCYTES. S. BERGEL, Virchows Arch. f. path. Anat. **266**:820, 1928.

The author states that lymphocytes have a lipolytic function, whereas leukocytes do not. Lipoid substances are seen to be taken up and digested by lymphocytes, which therefore are of greatest importance in tuberculous and syphilitic infections. There is no parallelism, however, between the number of lymphocytes and the lipase content of the blood. The lipase is specific for the antigen which calls it forth.

B. R. LOVETT.

CERTAIN FEATURES OF THE MORPHOLOGIC PATHOLOGY OF ENDEMIC GOITER. D. MARINE, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-27, 1927. Edited by Hans Huber, Bern, 1928.

The cycle of morphologic changes in the thyroid is essentially the same in all animals and consists of hypertrophy and hyperplasia followed either by exhaustion atrophy (cretinism and myxedema) or by involution to the colloid or resting stage (recovery). Exhaustion atrophy occurs only in the severest grades of uncompensatory hyperplasia, while involution to colloid goiter is the usual termination of active hyperplasia.

Of the numerous secondary changes that occur in goiter, the development of adenomatous nodules is most prominent in goiter in man. Struma nodosa is rarely seen in the lower animals. The belief is expressed that these nodules arise from differentiated thyroid tissue during the late stages of compensatory hypertrophy because of different rates of growth. These nodules tend to repeat the same morphologic cycle as nonadenomatous tissue although somewhat modified. There is abundant evidence that these adenomatous growths can produce thyroxine. There is no evidence that true tumors can produce this substance.

Thyroid hyperplasia (goiter) is a compensatory process dependent on a relative or absolute deficiency of iodine.

AUTHOR'S SUMMARY (A. HELLWIG).

PATHOLOGIC ANATOMY OF THE MALIGNANT GOITER AND OF THE THYROID GLAND OF CRETINS. C. WEGELIN, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-27, 1927. Edited by Hans Huber, Bern, 1928.

The malignant tumors of the thyroid gland are far more frequent in countries in which the goiter is endemic than in goiter-free regions.

The epithelial forms of the malignant goiter may be designated as carcinoma from a biologic point of view. Their malignancy is chiefly evident by the formation of metastasis. Histologically these neoplasms are often not ordinary cancers, but more differentiated and typically formed tumors which also always appear in the form of nodules. The highest degree of differentiation is reached by the metastasizing adenoma, a lesser one by the Langhans' proliferating adenoma and the least degree by the simple carcinoma. There are transitions which unite all these forms. They metastasize only after invasion of the blood vessels especially of the capsular veins. The age of the patient must be considered as another important factor.

The malignant epithelial neoplasm, as well as the sarcoma and hemangioendothelioma, often originate in the nodules of old adenomas.

The study of histogenesis thus shows a connection of the malignant tumors with the common endemic nodular goiter. Efficacious prophylaxis of the goiter will therefore be able to diminish the incidence of malignant goiter.

Endemic cretinism is to be found only in districts in which goiter is endemic and in which the endemic has reached a high degree.

The thyroid of the cretin contains, as a rule, adenomatous nodules which, however, vary greatly in size. Almost without exception, they are parenchymatous and contain little or no colloid.

The structure of the thyroid tissue proper between the nodules shows characteristic changes, the epithelial cells undergoing a more or less severe degeneration. The colloid of the acini is scanty, chiefly basophil and the connective tissue is increased, forming a marked sclerosis. These changes are found in the highest degree in the atrophic thyroid glands of dwarf cretins.

The degeneration of the epithelial tissue of the gland begins early in the cretin. His thyroid gland functions in an inferior way, although part of its functions may be taken over by the adenomas.

The whole organism of the cretins is influenced by a hypothyroidism of different degree. The changes in the other organs show considerable resemblance or conformity with the changes seen in congenital or acquired athyreosis.

Regarding the etiology of endemic cretinism, external injuries of the thyroid gland, as well as hereditary factors, must be taken into account. The nature of the external factors is not yet known. The assumption that cretinism is a recurrence to the type of the primitive human races is not proved.

AUTHOR'S SUMMARY (A. HELLWIG).

ANATOMY OF GOITER. L. ASCHOFF, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

In order to understand the morphologic and etiologic genesis of goiter it is necessary to grasp the fact that the biologic curve of the goitrous thyroid is parallel to that of the nongoitrous thyroid gland. The curve of the goitrous thyroid is, however, more elevated than the other. From the morphologic point of view, goiter is a real hyperplasia of the thyroid.

In the curves of age incidence, there are several corresponding sharp rises to be noted, viz., the swelling or goiter of infancy, puberty and advanced age. In point of origin, they are to be distinguished as follows: (*a*) in the goiter of infancy, there is in addition to increased new formation a simultaneously increased moisture of the whole parenchyma. (*b*) The swelling or goiter of puberty is of chief importance, since on its degree essentially depends the intensity of the later

developed adenoma. (*c*) In advanced age, a retrogression of the proliferating goiter of goiter may come to pass.

The biologic curve of the thyroid, goitrous or otherwise, is deformed by the development of the so-called adenomas. The germ of them occurs in all thyroids. In districts in which goiter seldom occurs they develop slowly and only to a certain size, in goitrous countries much faster and on occasion up to the size of a child's head or even larger. This intensified development of the tumors, the so-called struma nodosa, depends especially on the enhanced metabolism of the goitrous thyroids.

In point of histologic origin, the adenomas present either an unphysiologic growth with immature (parenchymatous goiter) or riper stages (colloid goiter). According to the type of involution to which these tumors generally tend, the names of fibrous, calcified, hemorrhagic, cystic goiter are given. The nodular goiter originates commonly at or after puberty.

The question of etiology must be considered with that of the source of the general increase in weight of the thyroid in goitrous regions. Comparative histology supports the view that here an exogenous factor encountered in the surroundings is at fault, which leads to enhanced physiologic growth. According to chemical analysis of goitrous and nongoitrous thyroids, it must be assumed that the thyroid as a whole is continually striving for certain iodine content. When the supply is deficient, the absorbent surface of the thyroid increases through further growth of the parenchyma. Conformably thereto the percentage of iodine content is similar in the goitrous thyroid. Experiment indicates that it is not simply iodine deficiency which comes into play, but disturbed equilbrium between iodine and other substances.

The question of the periodic swelling or increase in size of the thyroid (that of pregnancy, infancy, puberty, advanced age and their respective forms of goiter) is independent from that of the goitrous swelling. Here factors at once endogenous and physiologic — among them perhaps an insufficiency of iodine metabolism or disturbances of iodine equilibrium connected with growth — have to be reckoned with.

A sharp distinction must be drawn between endemic goiter and the thyroid of exophthalmic goiter. In this case the causative factor is endogenous and, in contrast to the swelling mentioned, pathologic. Simultaneous diseases of the thymus, suprarenal glands and lymphatic system warrant the conclusion that this cause attacks the nervous system and not the thyroid. The thyroid in cases of exophthalmic goiter is characterized by a special hyperplasia in the interior of the individual follicles. Intermediate stages occur between the hyperplasia in exophthalmic goiter and the parenchymatous goiter.

In contrast to the thyroid of exophthalmic goiter which shows marked symptoms of hyperthyroidism, in the goitrous thyroid it shows rather the picture of hypothyroidism in all stages down to complete cretinism. Only in a few cases does goiter exhibit hyperthyroidism; such are usually late forms of the goiter of puberty or so-called toxic adenoma.

Provided no signs of cretinism occur, endemic goiter displays no secondary influence on other systems. Goitrous heart, implying that the heart muscle is damaged by thyroidal toxins or bacterial toxins, is, according to morphologic evidence, nonexistent.

AUTHOR'S SUMMARY (A. HELLWIG).

Pathologic Chemistry and Physics

LIPID STUDIES IN XANTHOMA. U. J. WILE, H. C. ECKSTEIN and A. C. CURTIS, Arch. Dermat. & Syph. **19**:35, 1929.

There is an excess of fatty substances other than cholesterol in the lesions of xanthoma. The cholesterol amounts to only 16 per cent of the entire content of lipids and only 2 per cent of the content of solids. Xanthoma frequently occurs

without cholesteremia. Xanthoma is not due primarily to cholesterol, for this substance occurs in the lesions in a normal value, whereas the other lipids are in increased amounts. The high cholesterol content of the blood in the lipemia of diabetes is an associated factor in the disordered fat metabolism and not the primary cause of xanthoma. In the absence of diabetes, marked increases in the alimentary fat do not appear to influence the formation or growth of xanthoma lesions. Apparently, the best treatment for xanthoma, with or without glycosuria, is a restricted diet as with obesity.

·AUTHORS' SUMMARY.

THE REACTION OF THE BLOOD IN CANCER. H. MILLET, J. Biol. Chem. **82**:263, 1929.

The hydrogen ion concentration of the blood in persons with cancer appears to be within the normal range.

ARTHUR LOCKE.

EFFECT OF DISEASE ON THE LIPID DISTRIBUTION IN HUMAN LIVER TISSUE. E. R. THEIS, J. Biol. Chem. **82**:327, 1929.

Normal liver tissue in man has a phospholipid neutral-fat ratio of approximately 3/2. This ratio becomes progressively decreased during the advance of pneumonia, tuberculosis and fatty degeneration.

ARTHUR LOCKE.

RELATION OF CHROMATIN TO HEMOGLOBIN AND BILIRUBIN. HERMAN H. RIECKER, J. Exper. Med. **49**:937, 1929.

Attention is directed to the diversity of opinion among investigators regarding the site and the manner of the formation of hemoglobin in the body, and its relation to bile pigment metabolism. It is probable that, in forming new hypotheses on this subject, the earlier work of A. B. Macallum on the relation of chromatin to the formation of hemoglobin has not received sufficient consideration. It has been shown by means of microchemical stains of the bone-marrow cells for iron, that the iron content of the hematoblast is increased during the rapid production of hemoglobin in simple anemia. This fact is compatible with the work of Macallum, who believed that hemoglobin is derived from the chromatin of the hemoblast. It does not support a theory that hemoglobin is formed as a part of a circulating pigment. It is suggested that bilirubin is derived from the chromatin of body cells through the intermediary stages of the respiratory pigments, hemoglobin and cytochrome, from erythrocytes and other cells, respectively.

AUTHOR'S SUMMARY.

PHYSIOLOGIC CHEMISTRY OF SENESCENCE OF TISSUES (CORNEA). M. BÜRGER and G. SCHLOMKA, Ztschr. f. d. ges. exper. Med. **61**:465, 1928.

Previous contributions dealt with chemical changes in cartilage and lens during senescence. The main changes found were diminution of water content and deposition of cholesterol, calcium and other substances. Similar results were obtained in examination of the cornea in cattle. There was demonstrated a progressive diminution of the water content and a corresponding increase of dry substance. The nitrogen content of the dry substance was decreased, the cholesterol content increased. The authors believe that the formation of arcus senilis is determined primarily by condensation of the tissue (diminution of water content) and secondarily by deposition of cholesterol and lipoids. This view is opposed to that of Versé and his collaborators, who regard the formation of arcus senilis primarily as an expression of disturbed cholesterol metabolism.

BALDUIN LUCKE.

THE POTASSIUM, CALCIUM AND MAGNESIUM CONTENTS OF CEREBROSPINAL FLUID. BELA EISLER, Ztschr. f. d. ges. exper. Med. **61**:549, 1928.

The potassium, calcium and magnesium contents in the cerebrospinal fluid and their relative ratios were determined for 154 patients. In the acute, purulent forms

of meningitis (twenty-nine cases), little change was found in the amounts of potassium and calcium, but the amount of magnesium was increased several fold. In tuberculous meningitis (fifteen cases) there was an increase of potassium to from 15 to 20 per cent above the normal, and a diminution of calcium. No changes were found in twenty-eight cases of serous meningitis. There were no constant changes in thirty-eight cases of cerebrospinal syphilis. In two cases of paresis there occurred an increase of potassium and magnesium, and a decrease of calcium after treatment with malarial parasites. In patients with tetany and spasmophilia, the calcium was particularly low.

BALDUIN LUCKE.

RELATIONS OF BLOOD PRESSURE, BLOOD VOLUME AND SIZE OF HEART. ALFRED BEHRENS and WALTER LAMPE, Ztschr. f. d. ges. exper. Med. **61**:651, 1928.

From clinical and roentgenologic observations, it is apparent that the size of the heart depends to a certain degree on the blood volume. Thus, in nearly exsanguinated patients (hemorrhage from gastric ulcer), the cardiac shadow increased in size as the general condition improved; this change in cardiac size cannot be explained as hypertrophy. The interrelation of blood pressure, blood volume and size of heart was investigated experimentally in dogs and rabbits. In these animals, a diminution of the blood volume (through venesection) led to a reduction in the size of the cardiac shadow and to a lowering of the blood pressure. A return to the normal could immediately be brought about by an intravenous injection of colloidal solutions, such as acacia. A sudden increase of blood volume was obtained by the rapid intravenous injection of 20 per cent acacia and similar solutions; this led to an increase of cardiac size and a rise in blood pressure.

Gradual injection of fluid did not alter blood pressure or cardiac size.

BALDUIN LUCKE.

POSTMORTEM ACIDITY OF THE BLOOD. OTTO GSELL, Ztschr. f. d. ges. exper. Med. **63**:18, 1928.

Electrometric determinations of p_H were made on the blood obtained post mortem from a series of patients and laboratory animals. It was found that a definite decrease of p_H occurs after death. The greatest increase in acidity takes place in the first hour after death; after from three to four hours, a maximum is generally reached at which the p_H is approximately 1 less than it was immediately before death. Corresponding changes in the hydrogen ion concentration are to be found in the various organs. The changes in the blood are due to diffusion of acid from the various organs. The p_H decrease in the first hour after death is to be attributed to the anoxybiotic phase of carbohydrate metabolism, which continues for a short while after death, and hence represents the final expression of vital processes. Rigor mortis, postmortem clotting of blood and possibly the clouding of the parenchymatous tissues are the sequels of postmortem acidity. From about the fourth to the sixth hour after death, the hydrogen ion concentration of the blood undergoes no constant change; there is sometimes a shift toward the alkaline, at other times a shift toward the acid region. These fluctuations are determined by autolytic processes. It follows that p_H determinations made three or four hours after death will not give constant results.

BALDUIN LUCKE.

PATHOLOGY OF BLOOD PROTEINS. G. VON FARKAS, Ztschr. f. d. ges. exper. Med. **63**:64, 1928.

Total plasma protein was determined by Kjeldahl's method; the relative proportions of the fractions (albumin, globulin, fibrinogen) were estimated by nephelometric methods. The author emphasizes that marked fluctuations may occur even during health. He gives a table to show the variations observed in healthy adults (number of persons examined is not stated): total protein, from 6.1 to 8.7 Gm.

per cent; albumin, from 3.6 to 5.5 Gm.; globulin, from 1.4 to 3.9 Gm.; fibrinogen, from 0.2 to 0.3 Gm. Two examples of diurnal variation are given, showing slight fluctuations of the various values. In patients with compensated cardiac disease, normal levels were found. In those with decompensated cardiac disease with edema there was reduction in the total amount of protein (total protein, 5.87 Gm.; albumin, 3.4 Gm.; globulin, 2.22 Gm.; fibrinogen, 0.53 Gm.). In cases of nephrosis there was the usual reduction of total protein with an absolute reduction in albumin, and an increase in globulin and fibrinogen. In some cases of cachexia (a case of severe tuberculosis is given as an example), the total protein may be increased to over 10 Gm. per cent.

In cases of hypertension of nephrogenic origin (nephrosclerosis) there was an increase in total protein due to increase in the albumin fraction.

After injection of antigens there occurred an increase in total protein, due, mainly, to an increase in the globulin and fibrinogen fractions. Similar results were obtained after intramuscular injections of sulphur.

BALDUIN LUCKE.

PHYSIOLOGIC CHEMISTRY OF SENESCENCE OF TISSUES (SKIN). M. BÜRGER and G. SCHLOMKA, Ztschr. f. d. ges. exper. Med. **63**:105, 1928.

Previous studies dealt with "bradytrophic" tissues, i.e., tissues (cartilage, lens, cornea) not possessing an independent blood supply and nourished by diffusion of fluids from adjacent tissues. The changes developing with age in such tissues were, primarily, a condensation, as evidenced by decrease of water content, and, secondarily, depositions of cholesterol, calcium, etc. The present study was undertaken in order to determine a possible chemical difference in a tissue having a rich blood supply, the skin. The material was removed from the upper thoracic region within twenty-four hours post mortem and the subcutaneous tissue was carefully dissected off. The water, nitrogen and cholesterol contents were determined. The water content was found to decrease with age; the nitrogen content showed but slight changes and the cholesterol content a definite and gradual decrease. This diminution of cholesterol is in striking contrast with the results obtained in the examination of cartilage, cornea and lens.

BALDUIN LUCKE.

THE IODINE CONTENT OF HUMAN ORGANS. BRUNO BUCHHOLZ, Ztschr. f. d. ges. exper. Med. **63**:188, 1928.

Extensive tables are given showing the results obtained by other investigators, as well as by the author. All tissues in man contain iodine, but there is no constant level of the iodine in the different organs, except possibly in the thyroid gland. The iodine of the thyroid gland constitutes from about 1/6 to 1/4 of the total iodine of the body. All glands of internal secretion contain a higher level of iodine than the other organs; this is particularly true of the ovaries and the suprarenal glands. There appears to be a definite relation between the iodine content and the functioning of organs of internal secretion; thus the ovary after the menopause practically loses its iodine content.

BALDUIN LUCKE.

PHYSICOCHEMICAL CHANGES OF THE BLOOD AND HISTOLOGIC CHANGES IN THE KIDNEY IN EXPERIMENTAL NEPHRITIS. N. ISHIYAMA, Ztschr. f. d. ges. exper. Med. **63**:699, 1928.

Determinations were made of the total serum protein and the protein fractions of the nonprotein nitrogen, and of the sedimentation rates of erythrocytes in a series of normal rabbits, as well as rabbits fed on a diet high in protein (a mixture of soja beans and a vegetable protein preparation called "legmon"). The daily amount of protein ingested by each animal over a period of from thirty-three to sixty-seven days was from 26.7 to 35.6 Gm. Normal values are given for ten adult male, and an equal number of female, healthy rabbits. (The values stated

include total serum protein, fibrinogen, euglobin, pseudoglobulin, globulin, albumin, nonprotein nitrogen and the sedimentation rates of the erythrocytes.)

No differences were found between the sexes, in contrast with the definite difference that is normally present in man. Histologically, the kidneys of the animals disclosed the following changes: hypertrophy and hyperemia of the glomeruli, atrophy of convoluted tubules and overgrowth of stroma (details are not stated). The urinary changes consisted of a diminution of urinary output, a slight albuminuria and, in some animals, a slight increase of nonprotein nitrogen. There was also an indefinite increase in total serum protein. No important changes were observed in the sedimentation rates of erythrocytes.

BALDUIN LUCKE.

EFFECT OF HISTAMINE SHOCK ON BLOOD CALCIUM AND POTASSIUM IN DOGS. GUSTAV KUSCHINSKY, Ztschr. f. d. ges. exper. Med. **64**:563, 1926.

During histamine shock, the potassium was found greatly increased in plasma, or serum; it was less markedly increased in whole blood. The calcium was increased in plasma and serum, but sometimes decreased in whole blood. These results correspond to changes observed in anaphylactic shock.

BALDUIN LUCKE.

CATALASE CONTENT OF THE BLOOD FROM DIFFERENT CAPILLARY REGIONS. F. VON KRÜGER, Ztschr. f. d. ges. exper. Med. **64**:680, 1927.

The catalase number of the blood was determined for adults and two boys by the micromethod of Bach and Zubkowa (*Biochem. Ztschr.* **125**:283, 1921). Blood from the lobe of the ear and from the tip of the finger had the same catalase content. Normally, the catalase number varied directly with the number of erythrocytes. The catalase index (catalase number divided by numbers of erythrocytes in millions per cent) of normal persons fluctuates within narrow limits (2.8 to 3.8); the mean value at 20 C. is 3.2. For a given person, the catalase index, under physiologic conditions, represents a constant. The results obtained are contrary to those of Bischoff (*Arch. f. Kinderh.* **82**:189, 1927), who reported considerable variations of the catalase content of the blood from different capillary regions. The present author attributes these variations to errors of method.

BALDUIN LUCKE.

THE REACTION OF CELLS AND TISSUES. HELMUT PETOW and ERICH WITTKOWER, Ztschr. f. d. ges. exper. Med. **64**:736, 1929.

Mice and guinea-pigs received repeated subcutaneous or intraperitoneal injections of various indicators (neutral red, phenol red, brom-thymol blue, brom-cresol purple, methyl red, alizarin, brom-phenol blue). The animals were killed thirty minutes after the final injection and the various organs were examined grossly, as well as microscopically, in free-hand or frozen sections and teased preparations. The cells exhibited changes in color within a few minutes after the preparations were made in the sense that the colors appeared turbid so that shades and tints could not be correctly estimated. Certain dyes, especially alizarin, remained unchanged after treatment of the tissue with formaldehyde, thus permitting the fixation of tissues prior to examination. This article is not suitable for abstracting because of the extensive details on the staining reactions obtained by different indicators and in different cells. However, it contains a wealth of information for those working with vital dyes. In agreement with the results obtained by Miss Schmidtmann (previously abstracted in the ARCHIVES), the p_H of most cells was found to lie between 6.5 and 7. In the kidney, the p_H of the cortical cells was fairly constant at about 6.7, while the reaction of the medullary cells varied greatly. An excellent bibliography is appended to this paper.

BALDUIN LUCKE.

Microbiology and Parasitology

TYPHOID INFECTION BY RECTUM. C. R. HENEY, Am. J. Pub. Health **19**:166, 1929.

Thirteen cases of typhoid fever are reported as resulting from the use of a rectal drip apparatus without proper sterilization. The original source was a patient who developed typhoid fever on the fourteenth day after admission.

PNEUMOCOCCI HITHERTO CALLED GROUP IV. GEORGIA COOPER, MARGUERITE EDWARDS and CAROLYN ROSENSTEIN, J. Exper. Med. **49**:461, 1929.

The pneumococci hitherto known as group IV have been separated into ten types which have been designated by Roman numerals from IV to XIII. These have been correlated as far as possible with the types described by others. The prevalence and mortality of cases due to each type have been estimated in the limited number of cases studied. Laboratory tests indicated that therapeutic antiserums for types I, II and III have little protective power against the recently separated types. Monovalent antiserums of high agglutinative and protective power were prepared in rabbits for each type. Several monovalent antiserums, each specific for a type, which are suitable for agglutination and experimental therapeutic use, have been obtained by immunizing horses. An antiserum prepared for one type had little crossprotective power against other types. A study of the possibility of preparing a suitable refined and concentrated polyvalent antiserum has been begun.

AUTHORS' SUMMARY.

LACTASE AND LIPASE OF THE COLON BACILLUS. LOUIS LOWENSTEIN, WILLIAM L. FLEMING and JAMES M. NEILL, J. Exper. Med. **49**:475, 1929.

Colon bacilli possess endocellular heat-labile lactase and lipase enzymes which remain operative in sterile filtered solutions of the intracellular substances obtained through physical disintegration of the bacillary bodies. The demonstration of the lactase and detection of the hexose products of its action constitute experimental evidence that hydrolysis of the disaccharide is the first step in the fermentation of lactose by colon bacilli.

AUTHORS' SUMMARY.

OBSERVATIONS ON THE OXIDATION-REDUCTION PROPERTIES OF STERILE BACTERIOLOGICAL MEDIA. RENÉ DUBOS, J. Exper. Med. **49**:507, 1929.

Sterile plain broth contains an active oxidation-reduction system, the characteristics of which have been analyzed. Intensity factor: Under petrolatum seal, the lot of broth used in these experiments reaches a reduction potential corresponding to reduced indigo disulphonate ($rH = 10$). All the indicators with a more positive E'_o are reduced, the others are not affected. It seems probably that fresh broth, which has not undergone oxidation by molecular oxygen, would give a higher reduction potential. Capacity factor: The maximum amounts of different indicators that can be reduced correspond to equimolecular concentrations. This seems to indicate either (*a*) that the broth does not contain several "independent" reducing systems (at least in appreciable amounts), or (*b*) that these hypothetic "independent" systems all have about the same reduction potential. Time factor: The different indicators of oxidation-reduction potentials are reduced in the order of the electromotive series. Nature of the system: The system seems to be reversible (this not excluding the possibility of irreversible autoxidations) and does not appear to be of the nature of a sugar. The relation of these phenomena to the cultivation of different species of bacteria will be reported later.

AUTHOR'S SUMMARY.

NON-HEMOLYTIC STREPTOCOCCI AND ACUTE RHEUMATIC FEVER. ROBERT N. NYE and DAVID SEEGAL, J. Exper. Med. **49**:539, 1929.

Blood cultures from twenty-five cases of acute rheumatic fever were negative for nonhemolytic streptococci of both the alpha and gamma types. Nonhemolytic (gamma type) streptococci were frequently recovered from the throats of patients with this disease. Similar organisms were recovered just as frequently from the throats of normal persons. Although these nonhemolytic streptococci were morphologically and culturally identical, not only among themselves, but also when compared with stock Small and Birkhaug strains, all, including the latter, have failed to show any noteworthy degree of homogeneity. Representative strains of these streptococci have proved to be relatively nonpathogenic for rabbits following intravenous injection. These organisms, with a few exceptions, have failed to produce soluble skin-reacting toxins comparable to Birkhaug's standard test toxin. The foregoing facts seem to invalidate the assumption that any of these nonhemolytic streptococci play a specific rôle in the etiology of acute rheumatic fever.

AUTHORS' SUMMARY.

THE INITIATION OF GROWTH OF CERTAIN FACULTATIVE ANAEROBES AS RELATED TO OXIDATION-REDUCTION PROCESSES IN THE MEDIUM. RENÉ DUBOS, J. Exper. Med. **49**:559, 1929.

The growth of many pathogenic organisms in plain meat infusion broth is possible only when a large inoculum is used. This requirement is much less strict when the broth cultures are incubated under anaerobic conditions, in fresh mediums recently boiled or autoclaved, in fresh mediums reduced by means of hydrogen, or to which small amounts of cysteine or of blood have been added. It is suggested that this can be accounted for by assuming that the bacterial species under consideration can multiply only in mediums the oxidation potential of which is below a critical value. The favorable growth conditions obtained by the procedures already enumerated may be attributed to the establishment of a proper reduction potential in the medium; the same result is obtained by using a large inoculum, owing to the reducing properties of bacterial cells.

AUTHOR'S SUMMARY.

THE RELATION OF THE BACTERIOSTATIC ACTION OF CERTAIN DYES TO OXIDATION-REDUCTION PROCESSES. RENÉ DUBOS, J. Exper. Med. **49**:575, 1929.

Oxidized indophenols and methylene blue (methylthionine chloride, U. S. P.) are bacteriostatic for pneumococcus and hemolytic streptococci of human and bovine origin, while the indigoes, malachite green and litmus are not toxic. 2-chloroindophenol, the most positive of the indicators of oxidation-reduction potentials used, is also the only one to have a bacteriostatic action on cheese strains of *Streptococcus hemolyticus*. Methylene blue and the indophenols are no longer bacteriostatic when present in a reduced form in a medium capable of maintaining them in such a condition. A comparison of these results with the growth in plain broth of the organisms studied suggests that the "inhibiting" dyes "poise" the medium at an oxidation potential outside the range in which the inhibited organisms can grow. The validity of this hypothesis is discussed. The significance of these observations for the use of dyes in therapeutics is considered.

AUTHOR'S SUMMARY.

TOXIC SUBSTANCES OF BACILLUS TYPHOSUS. GREGORY SHWARTZMAN, J. Exper. Med. **49**:593, 1929.

It is shown in this paper that homologous immune serums are able to neutralize the *B. typhosus* skin-preparatory factors. The neutralization experiments were performed on a large number of rabbits, at least ten rabbits which showed positive control reactions being used for the titration of each serum. The rabbits into

which the mixtures of *B. typhosus* culture filtrates with immune serums were injected can be divided into the following categories; those showing complete neutralization in highest dilutions (HN), those showing complete neutralization only in lower dilutions (LN) and those showing no neutralization (NN). The results indicate that the potency of a given serum as measured by the method already outlined has a direct relation to the reactions obtained in these groups of rabbits. For practical purposes, the highest dilution of the serum which gives complete neutralization of the *B. typhosus* skin-preparatory factors (HN titer) may be taken as the actual titer of the serum as expressed in terms of their neutralization. The occurrence of a phenomenon suggestive of the prozone reaction is demonstrated. It also appears that the filtrates possess an antigenicity equal to that of dead and live bacteria. The studies on normal serums bring out the fact that normal serums fail to neutralize the *B. typhosus* skin-preparatory factors unless agglutinins can be demonstrated for *B. typhosus*. No normal serums have thus far been obtained which neutralized the skin-preparatory factors yet contained no *B. typhosus* agglutinins, but there were serums which contained these agglutinins but failed to neutralize the skin-preparatory factors. Some of the normal animals whose serums failed to neutralize the skin-preparatory factors were subsequently injected with *B. typhosus* culture filtrate and responded with neutralizing serums of high titer. Several heterologous serums were also investigated, namely, scarlet fever, erysipelas, Shiga bacillus, Flexner bacillus, Mount Desert bacillus, *B. coli* and *B. avicida*. These did not neutralize the *B. typhosus* skin-preparatory factors. On the other hand paratyphosus A and B serums produced neutralization in various proportions. And the rabbits into which the serum-filtrate mixtures were injected could also be divided according to the results obtained into the same three groups as those with *B. typhosus* serums. It is not known yet whether this neutralization is a group reaction or whether the skin-preparatory factors are identical with those of *B. typhosus*. It would appear from these studies that a method is available for the quantitative titration of substances in the serum which neutralize the skin-preparatory factors of local skin reactivity to *B. typhosus* culture-filtrates. It should be emphasized that it is possible to control the individual susceptibility of rabbits to this phenomenon. The method should permit of considerable accuracy in the quantitative titration of the neutralizing properties of a serum when a standardized procedure is developed. Experiments are under way to determine whether the method can be applied to the preparation of therapeutic serums. Work is also in progress to determine the effect of specific antiserums on *B. typhosus* skin-reacting factors introduced by the intravenous route.

AUTHOR'S SUMMARY.

TRANSMISSION OF FOWL-POX BY MOSQUITOES. I. J. KLIGLER, R. S. MUCKENFUSS and T. M. RIVERS, J. Exper. Med. **49**:649, 1929.

Culex and *Aëdes* mosquitoes are capable of transmitting fowlpox from diseased to healthy susceptible chickens. The mosquitoes remain infectious for at least fourteen days following a meal on diseased fowls.

AUTHORS' SUMMARY.

HERPES ENCEPHALITIS IN CEBUS MONKEYS. HANS ZINSSER, J. Exper. Med. **49**:661, 1929.

Herpes virus, which ordinarily produces in *Cebus olivaceus* monkeys an acutely fatal encephalitis closely resembling in time, symptoms and pathology the acute, herpetic disease of rabbits, may — in more resistant individual monkeys — lead to a more prolonged malady which, while unquestionably produced with herpes virus, simulates with considerable accuracy the human disease of acute encephalitis, in symptoms, in course and in pathologic changes.

AUTHOR'S SUMMARY.

A Strain of Bacillus Abortus from Swine. Theobald Smith, J. Exper. Med. **49**:671, 1929.

The outbreak of infectious abortion in swine, probably the first reported from the eastern United States, was associated with a strain of *Bacillus abortus* growing rapidly on ordinary nutrient agar slopes without seal and presenting certain slight pathologic deviations from the bovine form of disease in guinea-pigs such as the occurrence of necrotic, suppurating foci in spleen and lymph nodes. Agglutination tests, comprising both cross-agglutination and absorption procedures, failed to distinguish the strain from the bovine type. The gross appearance of the fetuses from this outbreak was normal. The shreds of placentas obtainable indicated slight erosion of the chorionic epithelium and some exudation. The specific bacilli were widely disseminated in the tissues of the fetuses. The pathogenic action of this swine strain on guinea-pigs was evidently much feebler than that of most earlier swine strains as reported and it approached more closely that of bovine strains. The culture fed to a pregnant sow failed to produce abortion, possibly because of the advanced stage of pregnancy. The organism was not recovered from the uterus but was found in the sow's milk.

Author's Summary.

Differentiation Between Some Toxic Substances in Anaerobically Produced Autolysates of Pneumococci (Types I and II). Julia T. Parker, J. Exper. Med. **49**:695, 1929.

The necrotizing and lung-toxic principles present in certain anaerobically prepared autolysates of pneumococcus types I and II are similar in respect to extreme sensitiveness to heat and to oxidation, and to their ability to be neutralized by the same anti-autolysate serums. These two poisons differ, however, in their ability to be adsorbed or inactivated by red cells; the lung-toxic principle being adsorbed or inactivated by such procedure while the necrotizing principle is not. Since pneumococcus hemotoxin is present in the anaerobic autolysates and is also adsorbed by red cells, it seemed possible that it was this substance in the autolysates which caused the diffuse lesions in the lungs and death of guinea-pigs. However, it was found that the intratracheal injection of pneumococcus hemotoxin prepared by the method of Avery and Neill only occasionally produced the characterictic reaction caused by the intratracheal injection of the anaerobic autolysates. From these experiments, we believe, therefore, that the necrotizing and lung-toxic principles, and probably the pneumococcus hemotoxin also, are all separate entities in the anaerobically produced autolysates described.

Author's Summary.

Survival of the Virus of Poliomyelitis for Eight Years in Glycerol. C. P. Rhoads, J. Exper. Med. **49**:701, 1929.

An instance of successful inoculation of poliomyelitis virus after preservation for eight years in 50 per cent glycerol is reported. The virulence of the material injected remained essentially unchanged during this period. The fact that poliomyelitis virus will survive in glycerol for so great a period may be taken as further indication of the improbability of streptococci as the inciting organisms. Poliomyelitis virus would seem to vary in its resistance to glycerolation. The remarkable persistence of active virus outside of the body may have a bearing on the epidemiology of poliomyelitis.

Author's Summary.

Septic Sore Throat in 1928 in Massachusetts: Epidemiology. Herbert L. Lombard, J. Prev. Med. **3**:81, 1929.

There were between 925 and 975 cases and 48 known deaths in the epidemic of sore throat in "K," Massachusetts, in July, 1928. The attack rate was 221 cases per thousand inhabitants; the death rate was 9.6 per thousand inhabitants. The epidemic was caused by the transmission, through raw milk, of hemolytic streptococci from the infected udder of a cow. The method by which the cow

was infected is unknown, although some evidence points toward a milk handler who was sick. Among the regular users of the infected milk the attack was greater in females than in males, but it shows no significant differences in the various age groups. The incubation period of the disease averaged two days. Over 90 per cent of the cases occurred within an interval of two weeks. Contact probably was responsible for less than 5 per cent of the total cases, but it is impossible to establish this definitely.

AUTHOR'S SUMMARY.

THE INCUBATION PERIOD OF POLIOMYELITIS. W. LLOYD AYCOCK and ELIOT H. LUTHER, J. Prev. Med. **3**:103, 1929.

Data bearing on the incubation period of poliomyelitis have been collected from the following sources: milk-borne outbreaks; cases following tonsillectomy; isolated groups of cases in the same locality where contact could not be traced; cases in which a single known contact occurred; certain instances of multiple cases in families in which the individuals had separated before the onset of the disease; and an analysis of all cases observed in 1928 in Massachusetts, with known contact, in which an interval of separation had occurred prior to onset. In all cases in which the time of exposure can be set within narrow limits the apparent incubation falls within a period of from six to twenty days. In all cases in which the last exposure occurred less than six days preceding onset of the secondary case, the duration of exposure is such that the incubation period could likewise have fallen within these limits. In none of the observations reported in this paper was the incubation period necessarily shorter than six days. In some of these observations there is evidence that the infectious period of the disease may extend from the fourteenth day preceding the onset of symptoms to at least the fifth day of the disease. The incubation period observed in the experimental disease in monkeys following inoculation of fully active virus was most often six or seven days, but varied from four to fifteen days. Longer incubation periods were observed following inoculation of modified virus.

AUTHORS' SUMMARY.

THE TRANSFER OF TUBERCULOSIS BY DUST AND OTHER AGENTS. A. EVELYN AUGUSTINE, J. Prev. Med. **3**:121, 1929.

The evidence that has been collected suggests that the demonstration of virulent tubercle bacilli in dust collected from the rooms or clothing of patients with open tuberculosis may be used as a measure of the danger to which those in contact with the patient are subjected. Dust from the rooms or clothing of patients who keep themselves clean contain tubercle bacilli much less frequently than dust from uncleanly homes and people. Tubercle bacilli are recovered more frequently from the rooms of women than of men with open tuberculosis, and less frequently from the clothing of women than of men. These relations may be explained by the greater personal cleanliness of women and their inability, when ill, to keep their houses clean. Tubercle bacilli are recovered more frequently from the homes and clothing of colored than of white patients. The number of tubercle bacilli in the sputum of the patient is a factor in determining the presence or absence of tubercle bacilli in surrounding dust.

AUTHOR'S SUMMARY.

"FOOD POISONING" PRODUCED IN MONKEYS BY FEEDING LIVING SALMONELLA CULTURES. G. M. DACK, E. O. JORDAN and W. L. WOOD, J. Prev. Med. **3**:153, 1929.

Rhesus monkeys fed with living cells of two strains of the *Salmonella* group manifested definite and characteristic signs of "food poisoning": watery diarrhea and general malaise with, in some cases, loss of appetite. Recovery was prompt and apparently complete; the specific bacilli were not found in the blood stream. A second attack could be produced in the same animal after a short interval. Monkeys fed with equivalent heat-killed portions of the same suspension showed no symptoms. Likewise, feeding with living cells of *Proteus* and *B. coli* failed to produce any noticeable effect.

AUTHORS' SUMMARY.

THE PATHOGENICITY OF MORGAN'S BACILLUS. LEON C. HAVENS and CATHERINE RIDGWAY, J. Prev. Med. **3**:159, 1929.

A group of thirteen cases, presenting clinical symptoms in common, has been described. Evidence is presented pointing to Morgan's bacillus as the etiologic agent.

AUTHORS' SUMMARY.

THERMO-LABILE STREPTOCOCCAL TOXIN WITH CYTOLYTIC EFFECT ON LEUCOCYTES. HILDA A. CHANNON and J. W. MCLEOD, J. Path. & Bact. **32**:283, 1929.

The older work on streptococcal toxin in which the general toxic effects of actively hemolytic filtrates are described has been repeated and confirmed. A thermolabile toxin which has a marked lytic action on leukocytes is present in such filtrates when 8 to 10 hour serum broth cultures of actively hemolytic streptococci are used. It is this toxin rather than the thermostable skin toxin which is in all probability responsible for the marked invasive activities of the streptococcus in the animal body. No evidence has been obtained in these investigations to show that the cytolytic effects on red cells and leukocytes are due to distinct toxins. It is quite possible that the action on the leukocytes is evident only when the hemolysin acts in high concentrations.

AUTHORS' SUMMARY.

THE EFFECT OF GOLD PREPARATIONS ON RELAPSING FEVER. G. STEINER and V. FISCHL, Klin. Wchnschr. **8**:582, 1929.

The chemotherapeutic index of the disodium salt of 4-sulphonethylamino-2-goldmercaptobenzosulphonic acid and A69 in experimental infections of rats with African relapsing fever is considerably higher than that of neoarsphenamine. With prophylactic doses, the former preparation causes, in contrast with the hitherto known prophylactic ineffective gold preparations, a temporary suppression or attenuation of the infection. During the immune period it is possible with this preparation and A69, to destroy the spirochetes persistent in the central nervous system, while arsphenamine and its derivatives have no effect.

AUTHORS' SUMMARY.

THE ACTION OF BACTERIOPHAGES ON TYPHOID BACILLI. CURT SONNENSCHEIN, München. med. Wchnschr. **76**:355, 1929.

Specific bacteriophage conferred hemolysin (5 per cent goat's blood agar) properties to fifty-five old and twenty-five new strains of typhoid bacilli grown at 37 C., and none at 22 C. Typhoid bacilli considered nonhemolytic in cultures, like the other gram-negative organisms of the typhoid paratyphoid enteritides group, have a latent property for hemolyzing goat blood agar. The hemolysis occurred not only with the specific typhoid bacillus phage, but also with four polyvalent phages. No hemolysis was observed with paratyphoid B, Breslau, Gartner, and Dysentery (Flexner, Shiga) bacilli and polyvalent phages, although these acting on typhoid bacilli stimulated them to hemolysis. The hemolysis by typhoid bacilli probably is no function of the bacteriophage, but rather a property of the treated typhoid bacilli. The hemolysin effect on goat's blood agar, in addition to the simple phage reaction with specific diagnostic phages, can be applied in identifying typhoid bacilli. For human blood agar the bacteriophage conferred no hemolysin properties to fifteen strains of typhoid bacilli. The hemolysin effect can be used therefore in identifying the kind of blood. Among fifty-six stock strains of *B. typhosus* inoculated directly on goat blood agar there were two hemolyzing strains. Both of these contained, by subsequent tests, active typhoid bacillus phages. A larger material is necessary to determine if all typhoid strains associated with typhoid bacteriophage can be separated from those without, by their

hemolyzing growth on goat blood agar. Among twenty strains of *B. typhosus* recently isolated from the blood and feces, one hemolyzed blood, and it also contained bacteriophage.

AUTHOR'S SUMMARY (IN PART).

THE RESISTANCE OF THE SKIN AGAINST TUBERCLE BACILLI. O. N. PODWYSSOTZKAJA and M. A. LANNIKOWA, Ztschr. f. Tuberk. **52**:474, 1929.

Tubercle bacilli were rubbed into the depilated and slightly traumatized skin of guinea-pigs. It was found that when small amounts of bacilli were used, the skin did not show any alterations. Larger amounts caused the development of small nodular lesions and swellings of the regional lymph glands. In massive infections, ulcerations and massive swelling of lymph glands with generalized tuberculosis developed.

MAX PINNER.

EFFECT OF FAT-SPLITTING ENZYME OF GUINEA-PIG LUNG ON TUBERCLE BACILLI. D. KANÓCZ, Ztschr. f. Tuberk. **53**:124, 1929.

The author had previously shown that the pulmonary vein blood contains 30 mg. per cent less fat than the blood of the pulmonary artery. The difference was ascribed to the action of a lipolytic enzyme normally present in the lung. To test the hypothesis that such an enzyme might be a factor in the protective mechanism of the lung against tuberculosis, glycerin extracts of perfused normal guinea-pig lung were made. Such extracts had the property of reducing the fat content of normal guinea-pig blood serum and of removing the lipoid envelope of the tubercle bacillus. Bacilli thus treated are claimed to protect the animal against infection when used as a vaccine and to influence favorably the course of an already established experimental infection.

O. T. SCHULTZ.

Immunology

BLOOD VOLUME IN THE GUINEA-PIG DURING ANAPHYLACTIC SHOCK. C. K. DRINKER and S. WENT, Am. J. Physiol. **88**:479, 1929.

Using the writers' micromethod of blood volume determination in guinea-pigs sensitized to sheep serum, no changes in blood volume could be found accompanying the anaphylactic reaction, if complications due to asphyxia were prevented by careful adjustment of artificial respiration.

H. E. EGGERS.

PROTECTION TESTS WITH SERUM OF PERSONS RECOVERED FROM YELLOW FEVER IN THE WESTERN HEMISPHERE AND WEST AFRICA. N. P. HUDSON, J. H. BAUER and C. B. PHILIP, Am. J. Trop. Med. **9**:1, 1929.

It was found that an attack of yellow fever in man induced an immunity transferable to *M. rhesus*. The serum from seven recovered cases in West Africa and that from four cases of eleven tested in the Western Hemisphere protected *M. rhesus* against lethal doses of a West African strain of yellow fever virus injected subcutaneously. Experimental yellow fever was prevented by the use of serum from persons who had the disease in different epidemics.

H. E. LANDT.

THE COMPLEMENT-FIXATION TEST IN DIFFERENT CLINICAL MANIFESTATIONS OF TUBERCULOSIS. T. THJÖTTA and E. GUNDERSEN, Am. Rev. Tuberc. **19**:212, 1929.

Three hundred and twenty-five serums from patients with different manifestations of tuberculosis were examined for complement-fixing ability and are grouped under three headings, pulmonary, surgical and skin tuberculosis, the positive percentages in the three groups being 94.6, 44 and 12.3, respectively.

Only cases of pulmonary tuberculosis showed a relatively high percentage of positive tests. In the other manifestations the positive tests seemed to depend mostly on the presence or preexistence of tuberculosis of the lungs. The complement-fixation test in tuberculosis cannot be compared with the Wassermann test in syphilis, but rather with the same test in other bacterial infections when the specific microbe is used as an antigen.

H. J. Corper.

Non-Specific Agglutinins in Tuberculosis. Robert A. Kilduff and William W. Hersohn, Am. Rev. Tuberc. **19**:223, 1929.

Nonspecific, heterologous agglutinins may be produced in tuberculosis for micro-organisms of the typhoid group, and, infrequently, for *Bacillus proteus* X 19. There was no apparent relation between the presence or amount of agglutinins and the character or clinical course of the tuberculous infection. The occurrence of agglutinins for micro-organisms of the typhoid group is not per se conclusive evidence that they are nonspecific, or heterologous in origin, as, in a definite number of such cases, the patient will be found to have had typhoid fever or to have received antityphoid vaccine. Heterologous agglutinin production in pulmonary tuberculosis is of relatively infrequent occurrence and without apparent relation to the clinical course of the disease.

H. J. Corper.

A Clinical Study of Tuberculin Fractions Prepared from Non-Protein Culture Media. Frederick Eberson and Ernest Wolff, Am. Rev. Tuberc. **19**:327, 1929.

In the extension of earlier work in which the inadequency of old tuberculin was stressed and in which tuberculin fractions were prepared from nonprotein culture mediums, detailed analyses of different tuberculous and nontuberculous groups were made, and the conclusion was drawn that a tuberculin preparation described as T. E. (alcohol and ether insoluble) gives better results than ordinary old tuberculin and is more selective as a clinical test material. The preparation and use of this tuberculin fraction are described and discussed.

H. J. Corper.

Cases of Erythema Nodosum with Negative Tuberculin Tests. Elsa Lagergren, Am. Rev. Tuberc. **19**:447, 1929.

The author describes six cases of erythema nodosum and believes, as a result of her studies, that an unknown specific infection was the cause of the erythema nodosum.

H. J. Corper.

Antigenic Properties of Evaporated Milk. Oran I. Cutler, J. A. M. A. **92**:964, 1929.

Heat applied to cow's milk in the process of preparing evaporated milk does not appear to change the antigenic capacity of the casein as determined by anaphylactic reactions. Evidence has been found that there is an alteration in the antigenic properties of whey protein present in raw milk by the heat applied to it in order to evaporate and sterilize cow's milk by the usual methods employed. This is especially seen in a change of specificity, whereby heated whey proteins are less reactive in animals sensitized with raw or pasteurized milk, or with antibodies against pasteurized milk.

Author's Summary.

Anaphylactic Experiments with Globin. Henry Francis Holden, Australian J. Exper. Biol. & M. Sc. **5**:285, 1928.

The injection of horse globin does not induce fatal anaphylaxis in guinea-pigs. Experiments with the isolated uterus suggest that it becomes sensitive to a protein in the globin solution, which is neither stroma nor serum protein. Quantitative considerations render it unlikely that it is globin.

Author's Summary.

HYPERGLYCEMIA IN ANAPHYLACTIC SHOCK IN THE DOG. ISOLDE T. ZECKWER and J. ERNEST NADLER, J. Exper. Med. **49**:481, 1929.

Nine unoperated dogs showed a rise of blood sugar during anaphylactic shock. In six of these dogs the rise was 60 mg. or over. Six dogs in which one adrenal had long previously been extirpated and the opposite splanchnic nerve cut, showed a low preliminary level of blood sugar, and a relative rise of blood sugar during anaphylaxis, but of less degree than in the unoperated animals. In no case was it greater than 52 mg. Anocemia did not appear to be a complicating factor, as evidenced by determination of the oxygen content of the arterial blood before and during shock. The rise in blood sugar, which occurs in spite of the loss of adrenal activity, is probably due to the venous stasis of the liver seen in anaphylaxis in the dog, because this rise in blood sugar can be simulated in a normal non-sensitized dog by mechanically constricting the hepatic veins for a brief interval. There are, therefore, probably two factors responsible for the hyperglycemia associated with anaphylaxis in the dog, sympathetic stimulation by way of the splanchnic nerves involving the activity of the adrenals, and glycogenolysis resulting directly from venous stasis of the liver.

AUTHORS' SUMMARY.

THE TOXICITY OF HUMAN SERUM FOR THE GUINEA-PIG. SUSAN GRIFFITH RAMSDELL and I. DAVIDSOHN, J. Exper. Med. **49**:497, 1929.

There are indications of toxicity in all fresh human serum for the guinea-pig; this toxicity tends to disappear after forty-eight hours after bleeding, and its manifestations are strikingly similar to those of the heterophilic antibody in immune rabbit serum; and of an increased toxicity in the serum of human patients treated with antiserums; this is usually coexistent with the production of other antibodies; it tends likewise to disappear in time after treatment; differential absorption experiments indicate that its character is heterophilic, and its manifestations differ from those of anaphylaxis in that certain circulatory effects — hemorrhage and increased edema in the lungs and distention of the right heart — are added to the usual observations in true anaphylactic deaths.

AUTHORS' SUMMARY.

REACTIONS OF RABBITS TO NONHEMOLYTIC STREPTOCOCCI. C. L. DERICK and HOMER F. SWIFT, J. Exper. Med. **49**:615, 1929.

Accompanying and following the evolution of a secondary reaction in the skin of rabbits after inoculation with suitable doses of certain nonhemolytic streptococci there quickly develops a general state of hypersensitiveness or allergy toward these streptococci. This state is made evident by ophthalmic reactions following corneal inoculations, by much increased reactivity of the skin following intracutaneous reinoculations, and by lethal reactions, resembling tuberculin shock, following intravenous inoculations. In a given hypersensitive rabbit there is a rough parallelism in the intensities of these different kinds of reactions. This type of hypersensitiveness or bacterial allergy does not follow primary intravenous inoculation of rabbits with comparable doses of the streptococci employed. As the development of this type of hypersensitiveness or bacterial allergy seems to accompany the production of focal lesions of a certain intensity, it is probable that in these foci are produced the substances or conditions which lead to this type of bacterial allergy.

AUTHORS' SUMMARY.

THE ALLERGIZING CAPACITY OF DIFFERENT STRAINS OF INDIFFERENT STREPTOCOCCI. C. H. HITCHCOCK and HOMER F. SWIFT, J. Exper. Med. **49**:637, 1929.

The indifferent streptococci are remarkably efficient allergizing agents when inoculated intradermally into rabbits. This is revealed by the high percentage of secondary reactions which occur in the lesions resulting from the inoculation of small doses of these organisms, and by the relative frequency with which

positive ophthalmic reactions are obtained following sensitization with relatively small doses. This allergizing capacity is most marked in the organisms of Type I and least marked in the noninulin-fermenting strains of Group X. The different resultants emerging from variations in allergizing capacity of streptococci and reactivity of host are clearly demonstrated in this series of experiments.

AUTHORS' SUMMARY.

THE CHEMICAL NATURE OF THE CONSTITUENT IN FOWL SERUM RESPONSIBLE FOR NON-SPECIFIC PRECIPITATIONS. GEORGE S. SCHILLING, J. Immunol. **16**:439, 1929.

Examination of precipitated serums, nonprecipitated clouding serums and normal, nonclouding serums of fowls by means of the ultramicroscope revealed fat globules in all cases. The fat globules are present in greater quantities in precipitated and in nonprecipitated clouding serum than in nonclouding serum. Microchemical tests on the precipitates resulting in the agglutination system from the addition of clouding serums show that those precipitates contain quantities of neutral fats and fatty acids. Spontaneous precipitates in fowl serums which induce nonspecific precipitations of serologic antigens, carry a significantly higher iodized oil content than serums which do not produce the cloudy reaction; significant differences in their protein contents do not appear. The constituents in fowl serums responsible for these nonspecific precipitations are indicated to be lipoproteins and neutral fats.

AUTHOR'S SUMMARY.

THE CHANCES OF ESTABLISHING NON-PATERNITY BY DETERMINATION OF BLOOD GROUPS. SANFORD B. HOOKER and WILLIAM C. BOYD, J. Immunol. **16**:451, 1929.

From the frequency distribution of blood groups and the laws governing their inheritance the relative usefulness of blood-grouping tests in bastardy proceedings has been calculated with the following result:

Group of Accused Man	Percentage in United States	Probabilities
O	45	1/3
A	42	1/17
B	10	1/7
AB	3	1/2
Unknown	100	1/7

QUALITATIVE DIVERSITY OF AGGLUTININ RESPONSE AMONG DIFFERENT RABBITS TREATED WITH THE SAME COMPLEX ANTIGEN (STREPTOCOCCUS SCARLATINAE). SANFORD B. HOOKER, J. Immunol. **16**:463, 1929.

The results suggest that qualitative deficiency of antibody response to scarlatinal streptococci occurs rather infrequently among rabbits. It probably explains some of the discrepant reactions obtained by different investigators who have worked with the same strains. The fact that an immune serum may not faithfully and completely reflect the antigenic features of a complex inoculum receives additional confirmation as does the author's previous conclusion that the injected animal's individuality may constitute an important variable in experiments of this kind.

AUTHOR'S SUMMARY.

SYPHILIS WITHOUT CHANCRE AFTER BLOOD TRANSFUSION. E. CONSTANTINESCON and N. VATAMANU, Ann. de mal. vén. **24**:161, 1929.

A generalized papular and erosive syphilitic eruption developed in a woman seventy-five days after she had received a blood transfusion. The donor had a mixed chancre at the time of the transfusion.

ECHINOCOCCUS ANTIGENS. J. H. BOTTERI, Klin. Wchnschr. **8**:836, 1929.

Protein-free echinococcus antigens of human and animal origin are able to sensitize and cause cutaneous reactions, but are not able to arouse general anaphylaxis. The early reaction in the form of wheals is a sensitive but less specific allergic reaction, dependent on a functional disposition of the skin. Probably the active agents here are the alcohol-soluble simple protein substances. These seem to be identical with the dialyzable substances which pass through the intact echinococcus membrane and cause the skin allergy. The delayed reactions in the form of characteristic specific edema, and the manifestations of general anaphylaxis are caused by the whole antigens, which in vivo reach the circulation of the host from the hydatid fluids by injury of the echinococcus membrane. In complement-fixation the lipoid fraction of the antigen probably is chiefly concerned, with the skin reaction chiefly the protein fraction.

AUTHOR'S SUMMARY.

ANAPHYLAXIS BY THE FORMATION OF SERUM-ISO-ANTIBODIES AFTER REPEATED TRANSFUSIONS OF PATERNAL BLOOD (IDENTICAL GROUP). P. GYÖRGY and E. WITEBSKY, Klin. Wchnschr. **8**:195, 1929.

A child, after several transfusions of blood from the father without symptoms, had a severe anaphylactic reaction when another transfusion was made with the father's blood. The blood of both was in group O.

EDWIN F. HIRSCH.

PROTECTIVE SUBSTANCES IN EXPERIMENTAL SYPHILIS. ALFRED COHN, Klin. Wchnschr. **8**:886, 1929.

The injection of killed spirochetes into animals or into man stimulates the formation of immune substances against the organisms. Why these cannot be demonstrated under the usual conditions of infection needs further investigation.

AUTHOR'S SUMMARY.

BLOOD CHOLESTEROL AND RESISTANCE IN PULMONARY TUBERCULOSIS. V. HINZE, Ztschr. f. Tuberk. **52**:199, 1928.

The amount of blood cholesterol in infraclavicular tuberculosis infections is markedly decreased, to about 53 mg. per hundred cubic centimeters. During the period of the primary complex, the cholesterol is somewhat decreased, but rises in the secondary stage. In cases with good allergic response the cholesterol is above the average. In those with poor response it is below the average. Coincident with high cholesterol level, strong tuberculin skin reactions are found. There is no relation between the extent of the lesion and the amount of blood cholesterol.

MAX PINNER.

VARIATION IN COMPLEMENT IN EXPERIMENTAL TUBERCULOSIS OF GUINEA-PIGS. LILLY SANDSTRÖM, Acta path. et microbiol. Scandinav. **6**:97, 1929.

In guinea-pigs inoculated by means of tubercle bacilli, fairly regular variations in the complement content of the blood were observed, the titer falling after the inoculation, rising and then falling again toward the end of the life of the animal. Whether this is a specific effect due to the tubercle bacilli or a general reaction for foreign substances is not determined.

Tumors

THE RELATION OF CANCER TO OLD AGE. JAMES EWING, Am. J. M. Sc. **177**:461, 1929.

There are not sufficient data at present to determine the real influence of old age on cancer. Statistics, however, show that the greatest incidence of cancer occurs shortly after middle life and that the liability to the disease, which has

increased greatly during the last two decades, becomes more marked as age advances. Three conditions in the aged require special consideration in dealing with this problem, namely: (1) atrophy of the parenchyma of organs, (2) replacement fibrosis and (3) arteriosclerosis. No one of these is of constant occurrence and there are many complicating factors. Further study is necessary before any conclusions can be reached.

PEARL ZEEK.

CANCER OF THE LUNGS. FREDERICK L. HOFFMAN, Am. Rev. Tuberc. **19**:392, 1929.

Cancer of the lung is unquestionably increasing in modern civilized countries. While no entirely conclusive evidence is yet available, there are reasons for believing that the increased frequency is in some way connected with the modern development of road transportation and road conditions which aid in gross atmospheric pollution. There is no definite evidence that smoking habits are a direct contributory cause toward malignant growths in the lungs. Gas warfare and influenza appeared not to be direct contributory causes. The relatively predominating number of men affected is highly significant. There is apparently no relation established between the occurrence of tumors of the lungs and pulmonary tuberculosis.

H. J. CORPER.

THE TETRAPLOID NUMBER OF CHROMOSOMES IN THE MALIGNANT CELL OF THE WALKER RAT SARCOMA NO. 1. MARGARET REED LEWIS and JANE LOCKWOOD, Bull. Johns Hopkins Hosp. **44**:187, 1929.

The large spindle cell of the Walker sarcoma no. 1 is apparently the malignant cell. It has a peculiar large granular nucleus with a distinct nuclear membrane, and during division, which takes place by mitosis, approximately eighty-four chromosomes appear. The mononuclear cell present in the tumor does not differ from that found in other tissues. It divides frequently by mitosis, and the number of chromosomes present at this time is about forty-two, the same as that found in the somatic cells of the normal albino rat.

AUTHORS' SUMMARY.

THE RELATION OF SCABIES TO CARCINOMA. G. AMORMIMO, Arch. per le sc. med. **53**:241, 1929.

Rabbits may have scabies due to *Psoroptes cuniculi* Mègnin, which lives in the follicles and in the epidermis. There is produced hyperkeratosis and proliferation of the follicles, but in no case was atypical epithelial proliferation observed. The lesions studied by Borrel in scabies and interpreted by him as carcinomatous are regarded by the author as reactions of a chronic inflammatory nature.

RELATION OF MAMMARY FIBRO-ADENOMATOSIS TO BENIGN AND MALIGNANT TUMORS OF THE BREAST. H. KÜCKENS, Beitr. z. path. Anat. u. z. allg. Path. **80**:40, 1928.

A series of 86 surgically removed mammary glands studied by the author contained 12 examples of what he terms idiopathic fibromatosis (Reclus-Schimmelbusch's disease), 8 of fibromatosis with marked epithelial proliferation and 14 of fibromatosis with benign tumors, most of the latter being fibro-adenomas, 1 of fibromatosis with sarcoma and 20 of fibromatosis with carcinoma. In addition to these, for comparative study there were 4 examples of postinflammatory fibrosis, 2 of tuberculous fibrosis, 10 of solitary fibro-adenoma, 13 of primary carcinoma not associated with fibromatosis and 2 of primary sarcoma not associated with fibromatosis. In his preliminary discussion of fibromatosis, the author considers the diffuse and slowly progressing overgrowth of fibrous tissue the primary process which has its origin in part in local factors but to a greater degree in improper functioning of the sex organs, which have a relationship through hormones with the mammary gland. Cyst formation is secondary and is due to occlusion

of ducts by the fibrous tissue. Cyst formation helps to initiate epithelial proliferation. The elastic tissue of the mamma increases progressively with age but bears no relation to the fibromatosis. The benign tumors which may arise either singly or multiply in the breast in which Schimmelbusch's disease is present consist usually of both fibrous and epithelial tissue, either of which may predominate. They arise within the abnormal tissue as the result of factors which lead to localized overgrowth of either tissue element or of both elements. The epithelial proliferation may become so marked as to make it necessary to consider it precancerous. Carcinoma may arise from single or multiple foci of unrestrained epithelial proliferation, in which endocrine factors which originate in the sex organs play a part. The carcinoma may develop in tissue which is the seat of diffuse fibromatosis or in benign fibro-epithelial tumors which have arisen in such tissue. The cancerous epithelium may come from either duct or acinar epithelium. Its growth may be chiefly intraductal, when it may have papillary, glandular or solid character, or it may early penetrate the wall of the duct or acinus and form glandular or solid carcinomatous tissue. The author believes that fibromatosis is so frequently a precursor of carcinoma that suggestive epithelial proliferation should lead to radical operation.

O. T. SCHULTZ.

UNUSUAL TUMORS OF THE MAMMARY GLAND. H. KÜCKENS, Beitr. z. path. Anat. u. z. allg. Path. **80**:116, 1928.

A series of surgically removed mammary glands which the author used for a study of the relation of adenofibromatosis to tumor and which is reported in another article (*Beitr. z. path. Anat. u. z. allg. Path.* **80**:40, 1928) contained a number of unusual tumors which the author describes and discusses. There were three examples of epidermoid cyst, which the author says is rare in the breast. The cysts were the size of a bean and were situated in the subcutaneous tissue beneath the nipple. They had no connection with the surface epidermis. They were lined by epidermis, the innermost layers of which were hornified, and they were filled with fatty material that contained granules of calcium. No epidermal derivatives were present in the wall and none were present in the immediately surrounding tissue. The author derives the cysts from misplacements of the embryonic epidermal downgrowths which form the milk ducts. Two carcinomas of the breast, one the size of a pea and the other the size of a small hazelnut, are described because of their minute size. They were embedded in the adipose tissue of the gland and were found only after careful sectioning of the gland. There was no carcinoma elsewhere in either breast, but the mammary tissue was the seat of adenofibromatosis. The author calls attention to the ease with which such small, minute, malignant tumors might be overlooked. A hemorrhagic carcinoma, which was of medullary type, contained cystic cavities filled with old blood and degenerated tumor tissue. The hemorrhage was the result of trauma. In a psammomatous carcinoma of the male breast, the centers of the tumor alveoli were calcified. A carcinosarcoma consisted of glandular carcinoma alveoli embedded in spindle celled sarcomatous tissue, the latter predominating in amount. Metaplasia of carcinoma to sarcoma and intergrowth of two originally distinct tumors are considered as possible explanations, but the author thinks that the tumor arose as a carcinoma, which stimulated the stroma to malignant proliferation. The author claims that the literature contains only twenty cases of carcinosarcoma of the mammary gland; these are briefly reviewed. There was a case of primary carcinoma of the mammary gland in a woman who also had a carcinoma of the uterus; the latter was also considered primary. The author claims that there are only two previously reported cases of primary carcinoma of the mammary gland associated with primary carcinoma of the uterus.

O. T. SCHULTZ.

TUMORS OF THE THYMUS. A. MATRAS and A. PRIESEL, Beitr. z. path. Anat. u. z. allg. Path. **80**:270, 1928.

The authors describe in detail seven tumors of the thymus, occurring in persons whose sex and age were respectively as follows: a woman, aged 62; a man,

aged 28; a man, aged 33; a man, aged 56; a woman, aged 52; a woman, aged 60, and a man, aged 35. In two cases the tumor had caused no clinical symptoms, was encapsulated, microscopically was sharply delimited and histologically was benign. These were composed of epithelial reticulum, in which were moderate numbers of lymphocytes, usually most numerous about the blood vessels. A third tumor was purely epithelial in structure and contained no lymphocytes; although well delimited in the gross, it had led to metastasis in a regional lymph node. The remaining neoplasms were clinically and anatomically malignant; they metastasized to the pleura, lung and mediastinal and bronchial lymph nodes. Three of these were so rich in lymphocytes in many areas as to suggest lymphosarcoma. At the periphery, however, the characteristic large cell, epithelial reticulum, was evident. Such lympho-epitheliomatous tumors are the most characteristic ones of the thymus, since they contain both the lymphoid and the epithelial elements of the normal organ. The remaining neoplasm had the histologic appearance of a spindle and large round cell sarcoma. In places these cells were united into a reticulum which established their origin from the epithelium of the thymus. Lymphocytes were not numerous; they were scattered about diffusely, in places separating the cells of the reticulum. In view of the varied morphology which thymic tumors may show, and especially because of the frequent combination of both lymphoid and epithelial elements, they can be called neither sarcomas nor carcinomas. Thymoma might be the better designation. Under this heading three groups can be made: epitheliomatous, the tumors of this type being relatively benign; lympho-epitheliomatous, such tumors being invasive and malignant, and lymphoreticular, the tumors simulating sarcoma and being less malignant than the lympho-epithelial type. No evidence of a transformation of epithelial cells to those of lymphoid type, as has been described by some authors for the normal thymus, could be seen in the tumors studied.

O. T. Schultz.

Tumors of the Fifth Nerve and Gasserian Ganglion. F. Altmann, Beitr. z. path. Anat. u. z. allg. Path. **80**:361, 1928.

Altmann describes in detail two cases of tumor involving the gasserian ganglion and the trunk of the fifth nerve, one in a man, aged 31, the other in a man, aged 55. In the first case, the clinical diagnosis was tumor, probably osteosarcoma, involving the base of the skull. The neoplasm occupied the middle cerebral fossa of the base of the skull and grew backward into the posterior fossa. It involved both the gasserian ganglion and the trunk of the nerve so extensively that it could not be determined whether it had its origin in the ganglion or in the nerve trunk. In the second case the probable clinical diagnoses were tumor of the brain or cerebellar encephalitis. The tumor had its origin in the sensory portion of the trunk of the left fifth nerve and involved the ganglion secondarily. Its growth was chiefly posterior toward the cerebellopontile angle. The two tumors were histologically much alike and are considered neurinomas. The author pays particular attention to the regressive changes which had occurred and which he considers characteristic of neurinoma. These consist of edematous separation of the tissue elements, which may go on to pseudocyst formation as in the second case and may lead to pleomorphism of the cellular elements; hyalinization, especially of the perivascular fibrous tissue, and interstitial hemorrhage, the areas of hemorrhage undergoing organization and hyalinization. In the first case there was, in addition to these changes, considerable fatty change, which was associated with the formation of pseudoxanthoma cells which had phagocytosed the fatty detritus. Twenty-one previously reported solitary tumors of the gasserian ganglion or fifth nerve trunk are reviewed. Twelve of these were left sided and eight were right sided. Seventeen occurred in males and three in females. The age distribution by decades was as follows: 25 to 35 years, 6; 35 to 45 years, 2; 45 to 56 years, 9. Nine of the tumors are classified as neurinomas or neurofibromas, the author considering them all probably neurinomas, and twelve as neurocytomas. The tumors of the latter group arise within the ganglion itself, may contain newly formed ganglion cells and glia and are clinically and histologically the more

malignant. The neurinomas may arise from the nerve trunk itself, and apparently more often from the sensory than from the motor portion. Their growth is less rapid than that of the neurocytomas. New formation of axis cylinders apparently occurs. As a further contribution to the regressive changes which may occur in the neurinoma, Altmann adds the description of a neurinoma of the left second cervical nerve, which arose in the anterior root and showed the same regressive changes as were noted in tumors of the fifth nerve.

O. T. SCHULTZ.

URINOGENOUS METASTASIS OF RECTAL CARCINOMA. A. BÖGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:640, 1928.

The author reports a case of rectal carcinoma which invaded the ureter of one side at about its middle third. Obstruction of the ureter was not complete, but in the lying position there was some retention of urine in the pelvis of the kidney, without, however, any pyuria. Carcinoma metastases were present on the inner surface of the renal pelvis and in the papillae of the kidney. The author holds that the metastasis is due to carcinoma cells transported upward in the retained urine.

O. T. SCHULTZ.

EXCHANGE OF ELECTROLYTES BETWEEN TUMOR TISSUE AND SOLUTION. G. L. ROHDENBURG and A. BERNHARD, Ztschr. f. Krebsforsch. **28**:301, 1929.

In the experiments of Rohdenburg and Bernhard, small fragments of rat tumors of various kinds and control bits of normal rat liver, skin and other tissues were placed in isotonic electrolyte solutions of varying composition. The latter imitated as closely as possible the blood plasma of rats with growing tumors and of animals with regressing tumors. Variations in exchange between tissue and solution were detected by changes in the weight of the tissue. Tumor tissue tended to lose weight during the first hour and a half of immersion, especially in solutions of the composition of the plasma of rats with regressing tumors. After longer immersion the weight loss became equalized. The tumor tissue gave up sodium to the solution and took up potassium. Tumor tissue gave up a slightly greater amount of nitrogen than did normal tissue.

O. T. SCHULTZ.

NEUTRAL RED AND IODINE REACTIONS OF CANCER SERUMS. B. S. ACEVEDO, Ztschr. f. Krebsforsch. **28**:311, 1929.

The author tried the reaction described by Botelho on 436 serums, and the older neutral red reaction of Roffo on 150 serums. The first consists of the addition to serum of a measured amount of dilute nitric acid in normal physiologic solution of sodium chloride, followed by three successive additions of a solution of iodine in potassium iodide; a positive reaction, said to denote cancer, is indicated by the persistence of the precipitate formed. The formation of precipitate was found to vary with the protein content of the serum, necessitating refractometric determination of serum albumin and globulin. Neither of the reactions tried was found by the author to be specific for tumor. Each gave a fairly high proportion of positive results in the serums of persons free from tumor, and a still higher percentage of negative results in patients with cancer. The reactions depend, not on the presence of tumor, but on hydrogen ion concentration and chemical composition of the serum not necessarily characteristic of cancer.

O. T. SCHULTZ.

PSEUDOMYXOMA PERITONEI OF APPENDICEAL ORIGIN COMBINED WITH PSEUDOMUCINOUS CYST OF OVARY. E. SCHULZE, Ztschr. f. Krebsforsch. **28**:316, 1929.

This is the report of a case of pseudomyxoma of the peritoneum, resulting from perforation of a mucocele of the appendix. This condition was associated with a pseudomucinous cyst of the ovary, a combination which leads to discussion

of the difficulty of determining the origin of the peritoneal condition when both appendix and ovary are involved.

O. T. SCHULTZ.

EFFECT OF AVITAMINOSIS ON TRANSPLANTABLE MOUSE CARCINOMA. O. THIES, Ztschr. f. Krebsforsch. **28**:328, 1929.

Thies reviews the previously published experimental work relating to the effects of quantitative and qualitative food deficiencies to the growth or recession of tumors. The tumor used in his own experiments was a Jensen strain of mouse carcinoma. The mice were kept on a diet deficient in A and B vitamins, which were supplied to the controls in the form of cod liver oil or yeast or both. The state of vitamin deficiency produced had no demonstrable effect on the number of takes or on the growth or regression of the tumor. The period during which the mice were on the deficient diet before being inoculated was short, a fact which the author admits may have had some effects on his results.

O. T. SCHULTZ.

Medicolegal Pathology

FATAL PHENOBARBITAL POISONING. H. N. WRIGHT, Arch. Int. Med. **43**:85, 1929.

It was decided that phenobarbital killed a woman whose body was found in a room in Minneapolis about twenty hours after her death. Chemical quantitative isolation of phenobarbital (luminal) was accomplished in the Department of Pharmacology at the University of Minnesota. The method employed is described and recommended. The statement is made that this is the first death of poisoning from this drug reported, although about twenty nonfatal cases of poisoning have occurred. This seems rather surprising in view of the frequent deaths from the closely related veronal. The report is accompanied by a brief review of the literature.

E. R. LE COUNT.

DIAGNOSIS OF SPECIES BY MICROSCOPIC STUDY OF BONES. C. CANUTO, Arch. di antrop. crim. **47**:948, 1927.

Twenty-two small fragments of bone required examination for a medicolegal investigation. The greatest dimension of any one was less than 1 cm. They were fragile and well calcified, and biologic methods in fixing their source were impracticable. By measuring the diameter of the haversian canals in microscopic preparations they were identified as being from a human being. These channels in man have as their smallest diameter one of from 10 to 15 microns, whereas in bones of other animals the diameters are larger; in swine, 40 microns; in rabbits, from 70 to 75 microns, etc. Canuto describes the methods he employed.

E. R. LE COUNT.

EXPERIMENTAL STUDIES OF ALCOHOLIC INTOXICATION. V. M. PALMIERI, Arch. di antrop. crim. **48**:477, 1928.

Experimental studies on dogs as to the effect of alcohol on the speed of sedimentation of red blood cells, the nuclear lobulation of leukocytes, the leukocytic ferments and phagocytosis show that, following ingestion of alcohol, there is a decrease in the phagocytic power of the leukocytes, manifested not only by the phagocytic index, but also by the decrease in the percentage of the phagocytic elements. With the ingestion of increasing amounts of alcohol there is a considerable depression of the phagocytic functions. The author concludes that alcoholic intoxication influences the phagocytic power, to a degree parallel with the quantity consumed. The nuclear lobulation of the leukocytes in normal dogs remains more or less constant. Under the influence of alcohol, an alteration of

the normal nuclear appearance takes place, which, however, does not follow any definite rule. The changes are not due to direct action of the alcohol, but are purely functional, accidental and indeterminate. Interesting are the observations regarding the peroxidase reaction, which appears increased during the alcoholic intoxication and achieves its normal level about forty-eight hours after the ingestion of alcohol.

E. L. MILOSLAVICH.

TRAUMA AND LYMPHOGRANULOMATOSIS. A. GERONNE, Aerztl. Sachverst.-Ztg. **33**:243, 1928.

This disease was recognized in a man, aged 18, nine months after he was severely injured by an automobile. After being knocked down, he was pinned under the front axle, so that some crushing of the chest occurred. If any of the bones of the thorax were broken, this escaped notice, since the head was also injured and a basal skull fracture suspected. Following the injury there was pain in both sides of the chest intermittently until glandular swelling was noticed, and during some of this period the sputum was bloody. In concluding that the accident had provoked the disease already latent to developing more rapidly than it would have without the injury, the following were important: that no other cause for the disease except the accident was obvious, and that the chain of symptoms between the injury and the disease was established, a thorough examination three months before the accident revealing only slight color blindness. Shortly after this expert opinion was given, the diagnosis of lymphogranulomatosis was confirmed by postmortem examination.

E. R. LE COUNT.

ACCIDENT, SUDDEN DEATH AND SYPHILITIC LEPTOMENINGITIS. W. WEIMANN, Aerztl. Sachverst.-Ztg. **33**:335, 1928.

While lifting a heavy drum (150 Kg.) on which wire was to be wound, two men fell but sustained no injury; the affair was not looked on as an accident, and the men finished their day's work. When one of them arrived home, he complained of abdominal pain and remained home the next day. On the third day, he went to a hospital but died on his arrival. The postmortem examination disclosed a generalized syphilitic leptomeningitis, markedly basilar, an intrapontile hemorrhage extending into the left cerebral peduncle and the entire brain stem as edematous. There were also aggregations of lymphocytes in the suprarenal cortices interpreted as syphilitic disease; the aorta was normal grossly. In reviewing the possibility of a connection between lifting the heavy drum and the hemorrhage and their bearing on compensation, it was decided that the occurrence in the factory had no relation to the sudden death, that the stomach ache was from chronic gastritis and that the hemorrhage would have been evident much sooner if caused by the strain of lifting or the fall. Many of the blood vessels in the leptomeninges, involved from without by the inflammation, were occluded by thrombi, some older than others. Death from spontaneous intracerebral hemorrhage without any preliminary coma is rare; but unexpected death from syphilis of the brain is observed more frequently.

E. R. LE COUNT.

GARAGE DEATHS. O. MARIENFELD, Aerztl. Sachverst.-Ztg. **34**:15, 1928.

This general review for physicians officially engaged in legal work and in insurance emphasizes the importance of investigating the garage and its equipment, the exact state of affairs in such places when persons are found dead in them, the open or closed doors and windows, ventilation, gas heating, electric wiring, temperature and other conditions of the machinery of the motor vehicles, the place where the body was found, just how the trunk and extremities lay, etc. The odors and smokiness of the vapors are also important and should be noted, if possible, before windows and doors are opened for airing. During 1926, the deaths in garages in Prussia numbered 242. Such deaths are not all from carbon monoxide. Some

are from benzine or benzol poisoning; others are electrocutions or from natural causes; many are accidental and some suicidal. Apparently, as yet, no considerable number have been homicidal.

Accompanying the exposition of such matters are many valuable suggestions regarding the postmortem examination of bodies of persons found dead in garages, although no attempt is made to present the pathologic anatomy of carbon monoxide, or of other, poisonings extensively. Public and private legal rights and details of liability for insurance and of the legal exemption for liability are also discussed. A number of references to unusual observations are included, some of them to hemorrhages and softening of the brain from carbon monoxide poisoning, and, according to the reports, with much less of an interval between poisoning and death than has been noted by most authorities.

E. R. Le Count.

Late Hemorrhage with Traumatic Rupture of the Spleen. P. Klassen, Aerztl. Sachverst.-Ztg. **34**:145, 1928.

Allusion is made with citations to reports by different writers of altogether fifteen deaths from intraperitoneal hemorrhage following traumatic rupture of the spleen, the intervals between injury and death being from one and a half to twelve days. The interval in Klassen's case, the sixteenth, was seven days; the injury was a blow from a piece of bread thrown by the wife of the patient. The external violence in these delayed bleedings is often slight, as this one was, and may attract no attention. In fact, questioning at great length may be required in learning of an injury. The tears are subcapsular for the interval, and the final break through the capsule into the abdominal cavity may be due to any one of a number of exertions, such as occur with lifting, coughing, vomiting, etc., by which the spleen is compressed by the diaphragm and wall of the trunk. With the stomach full, the concave surface of the spleen is supported and blows driving in the tenth rib, which has its long axis parallel with that of the spleen, tear the outer convex surface. With the stomach empty, the poles of the spleen are disposed to bend out, stretching the concave surface, so that the tears are in or just beneath the capsule about the splenic hilum. These late hemorrhages are especially important from the point of view of industrial insurance and of claims by laborers for compensation; for, after the violence, persons have been known to walk a mile without complaint; to walk home, then to a physician and finally to a hospital; to walk upstairs; to ride a bicycle or to carry burdens. A common symptom is pain in the left shoulder and left side of the thorax.

E. R. Le Count.

Death in a "Bleeder" from Occupational Strain. P. Kissinger, Aerztl. Sachverst.-Ztg. **34**:319, 1928.

The symptoms of weakness came on suddenly while the man in question was lifting cement blocks. He was 45 years old, and was known as a "bleeder," having had severe hemorrhages from simple cuts on his fingers, extraction of teeth, etc. He entered the hospital four days after his attack, complaining of weakness and tenderness in the right lower quadrant of the abdomen, where there was a swelling as large as a fist. He knew his condition and diagnosed his trouble. Since the accident he had become anemic; he died eighteen hours after entrance. A huge hemorrhage was found in the right iliac fossa retroperitoneal extending up so as to surround the right kidney. Its source was not found. Others have reported similar accidents in persons with hemophilia: one was a fatal intestinal hemorrhage in a man who had pressed with his abdomen on a lever; a second was a death from renal hemorrhage following a severe strain, and a third was a huge fatal hemorrhage in an obese bank official about the urinary bladder and adjacent structures, brought on by coughing.

E. R. Le Count.

INFECTION WITH SYPHILIS FROM POSTMORTEM EXAMINATIONS. P. MGALOBLISCHWILI, Dermat. Ztschr. **51**:167, 1927.

Among the conclusions of the author, these occur: The impression that syphilis cannot be contracted in working with cadavers is wrong; it may be contracted from bodies more than twenty-four hours dead; by making inquiries of directors of pathologic institutes, twenty well established cases were found, and fourteen that were probable; the chancre was on the digits in all but one of those cases, in which its location was learned, the exception being a case in which it was on the neck; in three persons so infected, the syphilis was malignant; errors in diagnosis were frequent; the greatest danger is in the bodies of infants and children with congenital syphilis.

E. R. LE COUNT.

CENTRAL TRAUMATIC HEMORRHAGE OF THE BRAIN. RENTER, Deutsche Ztschr. f. klin. Chir. **207**:92, 1928.

Deeply placed hemorrhages in such places as the internal capsule lenticular nuclei, pons or optic thalami may be caused by relatively slight violence. They may constitute the much disputed "late traumatic apoplexy." Caution is necessary in deciding whether apoplectic strokes coming on several weeks or months after a severe injury of the head are from spontaneous or from traumatic hemorrhage. When they occur after six months or later, they are probably due to trauma. Seven cases are reported.

E. R. LE COUNT.

IDENTIFICATION FROM REMNANTS OF SKELETONS. NIPPE, Med. Welt. **1**:1551, 1927.

An unknown man who killed himself was identified by the dental work he had received. Through the peculiarities of a second skull, indicating a mixture of the Slav and Tartar races, it was identified as that of a Russian prisoner of war who had disappeared. This led to the discovery that he had been murdered by his wife and a stepson, who were then executed. Another skull was identified as that of a soldier who had killed himself, by the evidence of an operation in the left frontal region. A fourth identification was made from the changes in the head of a right humerus, which indicated an extreme limitation of movement. This also resulted in the disclosure of a murder.

E. R. LE COUNT.

INDUSTRIAL INJURIES OF THE EYE. FUCHS, Wien. med. Wchnschr. **39**:1220, 1926.

According to statistics from different sources, from 20 to 38 per cent of blindness results from accidents. Of industrial accidents requiring compensation, injuries of the eye make up about 8 per cent. Those least dangerous are from carbon or metallic particles small enough to float in, or be blown about in, the air and to lodge in the eyes. The larger splinters of metal which are driven into the eyes from machinery cause more serious wounds. Among 1,000 workers in metals, 28 suffer some damage of vision and 16 lose one eye, according to some of the records. An infection of a nonpenetrating wound may cause the loss of an eye, and when fragments of metal become embedded in the eyeball without subsequent infection, blindness ultimately results without their removal.

E. R. LE COUNT.

THALLIUM POISONING. F. REDLICH, Wien. klin. Wchnschr. **40**:694, 1927.

With the intention of committing suicide, a young woman took a quantity of rat poison sold under the trade name of "Celio," or "Zelio," which contains 10 per cent of thallium sulphate. She suffered from intense pain in the legs, abdominal colic, vomiting and hyperalgesia and hyperesthesia of the legs. Sugar and albumin appeared in the urine. There was a lymphocytosis and three weeks

later the hair of the scalp came out in large masses. Previously, multiple neuritis and achylia have also been noted. Children are less susceptible than adults to thallium.

E. R. Le Count.

Occupational Anthrax. Rebentisch, Zentralbl. f. Gewerbehyg. **3**:162, 1926.

It was learned from insurance officials that during twenty years 648 laborers in the leather industries in Germany acquired anthrax and 98 died from the infection. The average number of persons employed each year was 37,274. The pustules in 93.2 per cent of the cases were on the exposed parts of the head, neck, arms or hands. The diagnosis was properly established in 95.7 per cent of the cases. Only 3.1 per cent of the infected skins were domestic.

E. R. Le Count.

Accidental Wounds and Other Injuries of Bursas. J. J. Wehrli, Inaug. Diss., Zurich, 1927.

Using the available information gathered for insurance records in Lucerne, beginning with 1923, the author found that 56.32 per cent of 522 cases of acute bursitis followed single injuries of considerable violence; in 25.67 per cent, the inflammation was purulent; in 83.8 per cent, healing took place in four weeks; in 8.9 per cent, healing was not complete at the end of two months, these all being purulent; 21.4 per cent of the cases were not concerned with occupations or industry; there were recurrences in 7.6 per cent; in 12.4 per cent, labor was not interrupted; in 55.17 per cent bursitis was of the knee, and in 42.9 per cent of the elbow. In only 6.51 per cent was the trouble caused by repeated trivial irritation, and chronic. These were practically all housemaid's knee.

E. R. Le Count.

Necrosis of the Heart from Radium. Wegelin, Schweiz. med. Wchnschr. **8**:895, 1926.

Two patients died suddenly from intrapericardial hemorrhage caused by necrosis of the heart wall and rupture, this, in its turn, being caused by radium treatment for esophageal cancer. In one, the radium bromide was in the esophagus seventy-two, in the other seventy-four, hours.

E. R. Le Count.

Technical

The Water Content of Blood Serum. Harvey Spencer, Am. J. Dis. Child. **37**:546, 1929.

The falling drop method is the most accurate of the several methods compared for measuring the water content in determining the specific gravity of the blood serum. The blood serum of patients exhibiting clinically the most marked dehydration had a higher specific gravity, a greater total solid content and a larger percentage of serum protein than the specimens from normal patients. The falling drop method of determining specific gravity is a procedure of clinical value, owing to its simplicity, accuracy and rapidity.

Author's Summary.

Culture Media from Commercial Dried Yeast. James M. Neill, John Y. Sugg, Lurline V. Richardson and William L. Fleming, J. Bact. **17**:329, 1929.

This paper describes the method of preparation of culture mediums from commercial dried yeast, and reviews their advantages and limitations. The "5 per cent yeast" broth and agar have been found satisfactory for all routine purposes for which meat infusion peptone mediums are commonly employed. The yeast

mediums are easy to prepare and possess the definite advantages of uniform reliability and low cost (9 cents per liter of broth). Their use is especially recommended for the routine culture of infectious material in clinical bacteriologic laboratories.

AUTHORS' SUMMARY.

AN IMPROVED METHOD OF CULTURE FROM A SINGLE BACTERIAL CELL. SYDNEY G. PAINE and J. C. RAMCHANDANI, J. Bact. **17**:377, 1929.

The method is a modification of the one given in an earlier number of the *Journal of Bacteriology* (Paine, 1927). Attenuations from the culture are made in five sterile watch glasses, as in the method of Paine, but, in place of sterile water, use is made of a sterile solution of nigrosine, as in the method of Burri. With the precautions described in the earlier paper, the appropriate dilutions are taken up with a steel mapping-pen, instead of being spotted on the surface of agar in a dish, are drawn in lines on the surface of a film of agar previously prepared on a long, narrow coverslip. In order to prevent ploughing up the surface of the agar, the steel pen is attached to its holder by a short coil of spring-brass wire. In this way, sufficient rigidity for the control of the pen's direction can be retained while allowing only the slightest pressure of the point of the pen on the surface of the agar. The coverslip is mounted above a glass slide, film side down, conveniently supported at the ends on thin strips of cardboard in such a way that contact of the agar film with the glass slide is just prevented. The ink lines are examined under the 12th inch objective, and the positions of what appear to be single bacterial cells are marked down by spots of Chinese ink. The slides are then placed in a moist chamber and incubated over night. Any colonies that develop at the marked spots from single cells will be of approximately the same size and may safely be assumed to be pure, while any that develop into larger than minimal size may be discarded as impure.

THE VALUE OF VEGETABLE EXTRACTS IN CULTURE MEDIUMS. LUTHER THOMPSON, J. Bact. **17**:379, 1929.

Aqueous extracts of potato, carrot, spinach, radish and beef heart were sterilized by filtration and added to nutrient broth aseptically. It was found that as little as 0.01 cc. of these extracts, when added to from 6 to 7 cc. of nutrient broth, would promote growth of many streptococci which did not grow in the broth alone, while 0.2 cc. was sufficient to give vigorous growth of most streptococci. Potato extract was found to be the most satisfactory because of its high nutritive value and because it keeps well without change in reaction or in precipitation of protein. Heat was found to have an effect on the extract proportional to the precipitation, those mediums giving the most precipitate being the least useful in accelerating growth. Both the proteid and nonproteid nitrogen fractions of the potato extract serve to stimulate growth of streptococci, but not in as marked a degree as the whole extract. Potato extract may be used in place of fresh blood in many instances in which it is not essential to observe hemolysis. It is helpful in getting a growth of streptococci and pneumococci free from cells and precipitated fractions of medium. As an enriching substance in ordinary fermentation tubes, it allows growth of streptococci without interfering with the action on the sugar. The substance in potato extract responsible for promoting growth is thought to be nitrogenous material, which furnishes suitable food for the bacteria, rather than food-accessory substances.

AUTHOR'S SUMMARY.

A NEW HISTOCHEMICAL METHOD FOR ARSPHENAMINE AND RELATED ARSENOBENZOL DERIVATIVES. N. VON JANCSÓ, JR., Ztschr. f. d. ges. exper. Med. **61**:63, 1928.

Tissues are fixed in solutions of formaldehyde (1 part of 40 per cent formaldehyde solution and 4 parts of distilled water) for from one to four days. Frozen sections are placed either in distilled water or in a freshly prepared silver bath

(to 1.5 per cent aqueous solution of silver nitrate, ammonium hydroxide is added, drop by drop, until the precipitate redissolves; to the clear solution an equal amount of purest glycerin is added). The sections are placed in this bath for from thirty to fifty-five minutes, care being taken to prevent their sticking together; the bath should be gently shaken. The sections are then washed in distilled water for about one minute and placed in a 1 per cent aqueous solution of sodium thiosulphate for from three to ten minutes; they are now transferred again to distilled water, dehydrated in the usual manner, washed in xylene and embedded in balsam. Arsphenamine and other arsenobenzol derivatives appear as brown or black granules. The method may be combined with nuclear staining (hematoxylin, alum carmine), staining for fats, etc. If minimal quantities of arsphenamine are to be demonstrated (as in human tissues after ordinary intravenous medication), it is advisable to place the sections for one hour in pure glycerin after the silver bath. (For further technical details the original paper and the author's previous publications, cited in the text, should be consulted.)

By means of this histochemical method, it has been possible to study the localization of arsphenamine and related preparations in the various tissues of man and animals. The author has shown that certain arsenobenzols are stored by the reticulo-endothelial cells. There were considerable and characteristic differences in the distribution of nine different forms of arsenobenzol derivatives. In general, these substances are distributed and stored like the acid vital dyes, such as benzopurpurin.

BALDUIN LUCKE.

THE DIAGNOSIS OF ENDOCARDITIS LENTA. H. KÜRTEN, Ztschr. f. d. ges. exper. Med. **61**:494, 1928.

A characteristic serum reaction in fifty-five cases of endocarditis lenta is described. To 1 cc. of serum in a test tube are added 2 drops of 40 per cent neutral solution of formaldehyde; the tube is shaken to produce thorough mixing, and is then allowed to stand at room temperature. During the next two hours, the presence or absence of gelation is noted by tilting the test tube. Kürten has examined the serums of over 1,100 patients and healthy persons by this test. Normal serums remain liquid for twenty-four hours; the serums from thirty-five cases of endocarditis lenta gelled either immediately or within two hours after the addition of solution of formaldehyde. The serums of five patients not suffering from endocarditis lenta (two with nephrosis, two with uremia and one with amyloid disease) gave a positive reaction. The author demonstrated that the reaction depends on an increase of the globulin fraction of the blood. While not specific, the reaction with solution of formaldehyde is of diagnostic value in cases of endocarditis lenta; other forms of endocarditis give a negative reaction.

BALDUIN LUCKE.

A NEW HISTOCHEMICAL METHOD FOR ARSPHENAMINE AND RELATED ARSENOBENZOL DERIVATIVES. JOSEPH SCHUMACHER, Ztschr. f. d. ges. exper. Med. **63**:804, 1928.

Schumacher calls attention to his publications on the demonstration of arsphenamine, which are not mentioned in the article by von Jancsó. References are given to his work. This is of interest in connection with the paper by von Janscó abstracted in the ARCHIVES.

BALDUIN LUCKE.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE

Joint Meeting, May 2, 1929

HARRISON S. MARTLAND, *Presiding*

NEW METHODS FOR THE SERODIAGNOSIS OF SYPHILIS. ERNST MEINICKE.

I shall say a few words about the old and new theories of the Wassermann reaction and the flocculation tests. The modern view of Sachs that there is a reaction between lipoids and antibodies against lipoids is at the bottom of all the reactions. The hypothesis of Klopstock is that the principle of the methods is an immunity reaction against the spirochetes and at the same time (combining his hypothesis with that of Sachs) an immunity reaction against lipoids. The new theories may be right, but they are not yet sufficiently proved. Nevertheless, the serodiagnostic methods have an ever-increasing practical importance in the detection of cases of syphilis and as a guide in treatment.

Until 1917, none of the flocculation reactions had practical importance. My Kochsalzmethode (sodium chloride method, M. R.) was the first which was proved to be of practical value. In 1918, Sachs and Klopstock followed with their reaction. In 1918, I published a second one, introduced in the literature as D. M. In 1921, Dold published the first turbidity test as a rapid test. I applied his theories to my own reaction and described my turbidity test, which as M. T. R. has extended widely throughout the world. New progress was made by Kahn and Muller. Both described reactions which were more sensitive than the old ones, and at the same time at least as specific. The International Serological Conference of last year at Copenhagen proved beyond doubt that both methods are more apt to fulfil the purpose of detecting cases of syphilis than the old methods. The Muller reaction is rather difficult to perform; the Kahn test, on the other hand, is not so difficult to set up, but there can sometimes arise some doubt in the reading of the results.

I therefore tried to develop and improve my turbidity test and to find a reaction as sensitive as possible and at the same time easy to perform and read. As a result of my investigations I published a reaction, called the Meinicke-Klärungs-Reaktion (M. K. R.) clarification reaction. The principle of this method is the clearing up of the mixture of serum and extract dilution, formerly opaque and milky turbid. The extracts used in this test are the same as in the M. T. R., only the amount of balsam of Tolu has been increased. (An exact description of the preparation of the antigen will be published in detail.) A short description of the performance of the test and the reading of the results was given.

The new test has been worked out lately (publication in print) as a rapid test and as a microreaction. In this form it is a flocculation reaction and not a clarification reaction. The principle is the formation of conglomerations in the positive cases, which can be easily observed through a microscope, using a small magnification of about 60 times. A short description of the performance of the micro test and of the readings was given.

In comparison with the Kahn test, the Wassermann test and the M. T. R. (turbidity test) with this new one in 3,000 cases, it has been shown that the Kahn test and the M. K. R. form one group of reactions which is much more sensitive than the Wassermann test and the M. T. R. There is a high percentage of positive cases in favor of the Kahn test and my new method. According to my experiences the clarification reaction is even more sensitive than the Kahn

reaction. In some positive cases it gives a positive result, whereas the Kahn test is negative or only weakly positive. The opposite occurrence is rather seldom. As at Copenhagen there are some exceptional cases, in which the old weak methods are superior to the new ones. Concerning the specificity, the new methods are more trustworthy than the old ones.

There can be no doubt that a sensitive method is of the highest value in detecting cases of syphilis. On the other hand, it must yet be proved whether the sensitive methods are not perhaps too strong to be a good guide during the treatment.

I venture to think it would be of great value to the scientists in this country in which the Kahn test is rather widespread to have now in my clarification reaction a simple method with which to check the Kahn test. In view of this I want to introduce my new tests into this country, and should be pleased to have them given a trial.

DISCUSSION

JOHN A. KOLMER, Philadelphia: It is highly probable, as Dr. Meinicke has indicated, that the antibody-like substance responsible for the complement-fixation reaction in syphilis is identical with that which causes the numerous flocculation reactions. It is also rather unfortunate that so much confusion has been developed in the serology of syphilis, particularly from the standpoint of the practitioner. Since Wassermann described his test in 1905, there have been developed a large number of modifications of his test, that usually bear his name, but many of these are indeed different, both in principle and practice, from the original Wassermann reaction, and many of the flocculation tests which have been developed since 1907 have been compared with the so-called Wassermann reaction without much attention being paid to the technic of the latter.

If one were to compare several of these flocculation reactions as described by Meinicke, Sachs, Dreyer, Kahn and others with the original Wassermann technic, it would be found that they are more sensitive and possibly a bit more specific, but one must compare these flocculation reactions with some of the newer and better complement-fixation tests for this disease. Furthermore, it is far more important to estimate the value of these flocculation reactions in relation to the diagnosis and treatment of syphilis than it is merely to compare them to the Wassermann reaction.

It is not true that these flocculation reactions are simple. They still have to be done by experienced serologists for acceptable results. It has been rather unfortunate that the literature on flocculation reactions has given a widespread impression that these are tests so simple that they can be done in the corner laboratory of the average physician's office. This is not true. These extracts have to be prepared with a great deal of skill, and the tests have to be conducted for the best results by experienced serologists.

We are not so much interested in how the flocculation reactions compare with the Wassermann reaction. We are far more interested in whether or not they improve the status of the serum diagnosis of this disease and as a control on its specific treatment. I think that the consensus in many circles is that none of the flocculation reactions have displaced the better of the complement-fixation reactions. This was the conclusion reached last May at Copenhagen in the Second Laboratory Conference of the Health Organization of the League of Nations to which Dr. Meinicke referred. It would appear that the consensus is that the complement-fixation test should be maintained, and that one or more of the flocculation reactions should be used as an additional test and as a control.

This is my own conclusion. My experience during the last few years has been based on the Kahn reaction, and I have not used the new Meinicke test. I did use his third method prior to 1923, and found that it agreed with the Wassermann reaction in about 90 per cent of cases. I have not had experience with the new modification that he has described this evening, but I find that the Kahn reaction agrees with my new complement-fixation test for syphilis in 96 per cent

of serums and that the difference of 4 per cent is made up of cases in which the patients react positively with the Kahn and negatively with the complement-fixation, or the reverse, with the general tendency for the Kahn reaction to remain positive longer in cases in which the patients were treated than the complement-fixation reaction.

The great difficulty with the flocculation test has been the reading and the interpretation of the weakly positive reactions, as estimated by Dr. Meinicke. It concerns a group of cases that are exceedingly important, because the cases are usually of so-called latent or concealed syphilis, or cases in which the patients have been treated and in which there is but a small amount of antibody in the blood. We want tests for the serologic diagnosis of syphilis that will clear up the doubt that usually surrounds the weakly positive reactions, and I must declare, so far as my own experience is concerned, that for the average serologist, the complement-fixation reaction is easier to read and much less likely to error of interpretation than are the weakly positive flocculation reactions. Furthermore, it has been my experience that the Kahn and other flocculation reactions do not ordinarily fare as well in the small laboratory with the average laboratory technician as does the complement-fixation reaction. If I can judge from the number of cases that are sent to me to untangle from the diagnostic standpoint, and more especially cases in which the diagnosis of syphilis has been made on the basis of a weakly positive Kahn reaction, I rather suspect that there are a good number of false positive reactions being recorded, so that I still believe that a good complement-fixation reaction is superior in the hands of the average laboratory technician than are several of the flocculation reactions. I have learned to view with some skepticism the significance of a weakly positive Kahn reaction, particularly those that give a —1, or a —11, because of the frequency with which they may occur in persons in whom syphilis can be excluded clinically. Of course the stronger reactions are just as specific as is the complement-fixation reaction.

Now, as far as a comparison of the Kahn with the complement-fixation test goes, these are best made when serums are carefully collected from groups of patients and tested in the laboratory without the serologist knowing anything about their source. One of the best studies in this connection was conducted in 1926 by Dr. Gilbert and Miss Langworthy, who sent serums to several different laboratories throughout the country, including my own in Philadelphia. In this group of 252 specimens from 227 patients, there were 24 cases of primary syphilis; 58 per cent gave a positive Kahn and 67 per cent gave a positive Kolmer complement-fixation. There were 6 cases of secondary syphilis, and both the Kahn and the complement-fixation reactions were positive in all of them. There were 24 cases of tertiary syphilis; 51 per cent gave a positive Kahn and 71 per cent a positive complement-fixation reaction. There were 21 cases of neurosyphilis; 70 per cent gave a positive Kahn and 80 per cent a positive complement-fixation. There were 30 cases of congenital syphilis; 37 per cent gave a positive Kahn and 40 per cent a positive complement-fixation. There were 105 cases of syphilis in which the patients were treated; 47 per cent gave a positive Kahn and 45 per cent a positive complement-fixation. These results are in line with our general experience in Philadelphia that the complement-fixation test is not really less sensitive. It is equally sensitive, and the two tests conducted together give the best information for the serum diagnosis of syphilis. In my opinion it is not a question of choosing one or the other. It is rather a realization that the serum diagnosis of syphilis is best served by choosing a good precipitation test in conjunction with a good complement-fixation test.

At this Second Laboratory Conference, held last May in Copenhagen, which I regret I was unable to attend because of my work at the University, there were 944 cases studied; 502 were syphilitic, 7 were doubtful and 435 were regarded as nonsyphilitic. Seven different complement-fixation tests were used, and about an equal number of flocculation tests, including the Meinicke test. In the complement-fixation tests, taking the Harrison technic for comparison, in 502 cases of syphilis, there were 58 per cent positive complement-fixation reactions,

including doubtfully positive reactions. In this group Meinicke reported about 56.5 per cent positive reactions. I do not know whether he used the method he talked about this evening or his former method, but his 56.5 per cent corresponded closely to the Harrison 58 per cent. The Kahn test came out much better, giving 67.5 per cent positive reactions. Sachs observed about 55.2 per cent positive reactions. Dreyer reported about 66.3 per cent positive reactions. Vernes, doing his rather complicated test, had 52.1 per cent positive reactions. It is equally important, however, to examine the percentage of positive reactions in cases in which the reaction was regarded as negative. Harrison, with the complement-fixation test, had about 2.7 per cent false positive reactions. Meinicke had 5 per cent false positive reactions; Kahn, 1.1 per cent; Sachs, 0.2 per cent; Dreyer (sigma test), 9.4 per cent, and Vernes had 10.5 per cent. Personally I am opposed to any test that yields falsely positive reactions. Every serologist knows that it is possible to make serologic technic hypersensitive and increase the percentage of positive reactions in syphilis, but that we immediately run the risk of getting false positive reactions in normal persons. I had far rather miss an occasional case of syphilis than to fasten the diagnosis of syphilis on a single nonsyphilitic person. When I devised my own modified complement-fixation test, I adjusted the hemolytic system in such a way that I felt reasonably sure we would miss an occasional case of so-called latent or concealed syphilis, but I had far rather do that than run the risk of getting false positive reactions in nonsyphilitic persons.

In conclusion, I may summarize one or two of the conclusions of this Second Laboratory Conference at Copenhagen, at which it was stated that "it desired to emphasize the fact that, no less than the complement-fixation tests, these flocculation methods are, despite their apparent simplicity, extremely sensitive to slight differences in experimental conditions and subject to so many sources of error, in connection both with the execution of the tests and in the reading and interpretation of results, that they must be placed only in the hands of specially trained serologists."

The Conference being of the opinion that some serologic tests may have the advantage of greater sensitiveness without being absolutely specific and vice versa, and that concordance of reaction of two or more tests has greater diagnostic value than has a single reaction "recommended that, in order to secure the most reliable information to the clinician, at least two different serologic diagnostic methods should be used." The Conference having in mind the necessity for constantly readjusting serodiagnostic methods in order to obtain the highest degree of specificity "recommended that the serologist should check the accuracy of his tests by regular and very frequent reference to the clinical data, in consultation with the clinician, whose assistance in supplying adequate information as to the history of syphilis and the clinical particulars of the case is of great value for the interpretation of the results." The Conference "wished to reiterate with particular emphasis that in spite of the increased sensitiveness which the various serodiagnostic methods have shown at the present Conference, serological results may, notwithstanding the presence of a syphilitic infection, be negative in certain cases; that a positive reaction in the absence of a clear history or of signs of syphilis should, if only to exclude all possibility of error, never be accepted until a test of at least one more specimen has afforded the same result; that except in the case of a few well defined pathological conditions, syphilis is indicated with a degree of probability which closely approximates its certainty when several tests performed according to different methods give a positive result."

As far as my own experience is concerned in serology and likewise in clinical syphilology, I believe that there is still a great need for the complement-fixation test. It is true there are certain times, particularly on board ships, when the complement-fixation test cannot be used, but otherwise the conduct of a complement-fixation test of acceptable accuracy and sensitiveness along with an acceptable flocculation test as a control would appear to serve best the serum diagnosis of syphilis.

ERNST MEINICKE: I may say that it was my old method I used at the last Conference in Copenhagen, and it was there that the tests of Kahn and Muller showed me it was possible to improve the method I had developed. The experience at the Conference was contrary to all opinions we had before. It was proved there that the most sensitive reactions, namely, the Kahn and the Muller tests, were the best concerning the specificity, and the Wassermann test in its several modifications came out well in the rear on account of the specificity. I am a bit skeptical, and we all were at the Conference, of the possibility of strengthening the Wassermann test or one of its modifications, in such a way that it can compete with the new tests, for at Copenhagen the Wassermann test had been worked out not only with inactive serum, but also with active serum, and it is known that a Wassermann reaction set up with active serum is much more sensitive than with inactive serum. I may state that it was the intention at Copenhagen to throw the Wassermann test out and to rely on the flocculation tests. The conclusion Dr. Kolmer referred to was not universal but the majority of the members voted that we ought to keep the Wassermann to check up with the flocculation tests. Some of the members of the Conference, however, were already in favor of the flocculation tests and against keeping the Wassermann test, and it was the impression at the Conference that, though the time had not come for discarding the Wassermann test, the probability was that we could do so, perhaps at the next Conference.

THE FUNCTIONS OF THE GALLBLADDER AND SOME OF THEIR DISTURBANCES IN THE LIGHT OF RECENT INVESTIGATIONS. BÉLA HALPERT.

The view most widely accepted regards the gallbladder as a reservoir, the function of which is to supply concentrated bile whenever there is call for such in the intestine. According to another view, of more recent conception, the bile enters the gallbladder not to be stored there and in time expelled, but to be resorbed in toto by the mucosa of the gallbladder (Sweet [Internat. Clinics **1**: 187, 1924], Halpert [Med. Klin. **20**:408, 1924], Blond [Arch. f. klin. Chir. **149**: 662, 1928]). Thus the gallbladder performs at least two main functions: first the return of important constituents of the bile into the circulation, and second by the resorption of bile, the relief and regulation of the pressure within the biliary system while the sphincter of the ductus choledochus is closed (Anat. Rec. **29**:359, 1925). There is considerable evidence, morphologic (Bull. Johns Hopkins Hosp. **40**:390, and **41**:77, 1927) and experimental, supporting this conception.

The first fold of Heister is a high thin semilunar membrane which narrows the lumen at the neck of the gallbladder to less than a third of the original diameter. The orifice is eccentrically situated. At the lower limb of the S-shaped turn of the neck of the gallbladder a second fold narrows the lumen. Here the neck continues into the cystic duct which tapers gradually toward its junction with the common hepatic duct. The crescent-like folds protruding into the lumen of the cystic duct are apparently arranged in a fashion to act as a system of "one way valves": they permit the inflow but prevent or hinder the outflow of bile from the gallbladder.

Data thus far obtained by studying the spontaneous contractions of the isolated gallbladder of the dog (Anat. Rec. **42**:50, 1929) indicate that the function of the muscular coat is that of preventing overdistention and to affect adjustment in size to the varying content. It was found that when the fluid content of the isolated gallbladder suspended in an oxygenated bath of Locke's solution at body temperature, was raised or lowered, a change was registered, but soon adjustment occurred and the curve returned to the previous level and resumed its former shape.

Experiments with methylene blue on the rabbit (Am. J. Physiol. **88**:351, 1927) prove beyond doubt that at least in this animal, and also in the rhesus monkey, when bile leaves the gallbladder through the cystic duct, this is rather an excep-

tion than the rule. These experiments also throw some light on the mechanism of the formation of gallstones. Abnormal composition of the bile or a disturbed resorptive function of the gallbladder mucosa leads to stagnation of bile in the biliary vesicle.

If stasis of stone-forming constituents in the gallbladder is due to an increased excretion of these elements or to a disturbed or altered functioning of the liver, we may speak of a "hepatogenous" stasis in the gallbladder. Experiments with methylene blue furnish a striking example of such a hepatogenous stasis (ARCH. PATH. **7**:473 [March] 1929). Injected intravenously or given by mouth, methylene blue appears in the bile and is poured into the gallbladder; the mucosa of the latter apparently cannot resorb the dye fast enough to cause its rapid disappearance, and so the dye stays there for days. It is evident that much the same thing happens when the sodium salt of tetraiodophenolphthalein is administered for cholecystography. Both of these examples of hepatogenous stasis in the gallbladder support the idea that something of the same order happens in cases of marked cholesterolemia, when the cholesterol content of the bile is correspondingly exaggerated.

If the stasis in the gallbladder is caused by intrinsic functional disturbances or demonstrable pathologic conditions of the gallbladder itself, with the functioning of the liver more or less unimpaired, one may speak of a "cystogenous" stasis in the gallbladder.

Perhaps the most convincing evidence for the existence of these two types, the hepatogenous and the cystogenous stasis, is furnished by the concretions usually found in these conditions.

The chemical composition and the architecture of gallstones permit their ready classification into three groups (ARCH. PATH. **6**:623 [Oct.] 1928). Those consisting purely or mainly of one of the stone-forming constituents of the bile, such as (*a*) cholesterol, (*b*) biliary pigments (calcium bilirubinate) and (*c*) calcium carbonate may be classed as group 1, i. e., the group of "pure gallstones." For the formation of all of these so-called "pure gallstones," the liver rather than the gallbladder may be considered primarily responsible. Group 2 is the group of "mixed gallstones," that is, those consisting purely or mainly of at least two of the constituents of the "pure gallstones." Their formation has generally been associated with infection. Infection and inflammation damage the mucosa of the gallbladder so that not all of the constituents of the bile are resorbed. Thus "mixed gallstones" are formed in cystogenous stasis in the gallbladder, the stagnation being responsible for the formation of the stones and the infection for the stagnation.

When a hepatogenous stasis in the gallbladder which has led to the formation of pure gallstones, precedes a cystogenous stasis, "combined gallstones" form, which have a nucleus formed by one of the members of the group of "pure gallstones" and have a shell formed by one of the members of the group of "mixed gallstones." If, on the other hand, a cystogenous stasis in the gallbladder which has led to the formation of mixed gallstones is followed by a hepatogenous stasis, "combined gallstones" form which have a nucleus formed by one of the members of the group of "mixed gallstones" and have a shell formed by one of the members of the group of "pure gallstones."

DISCUSSION

B. P. BABKIN, Montreal: Dr. Halpert emphasizes one of the functions of the gallbladder, and nobody, of course, denies this function. According to his opinion, bile which enters the gallbladder under normal conditions never leaves the gallbladder. I am afraid that there are many facts which speak against this theory. The greatest difficulty for Dr. Halpert is that his theory is in opposition to these facts. What are the facts that show that the gallbladder normally delivers its contents every day? The facts are these: We have a dog with a permanent Pavlov's fistula of the common bile duct. If there is no food in the alimentary tract of such a dog, there rarely comes a flow of bile from this fistula. As soon as food is given to such a dog, it will be seen that first of all there is a discharge

through this fistula of thick bile containing mucin. The content of solid matter in such bile is in many cases in the first and second hour twice as great as in the later hours; in the later hours, from the third to the sixth hour, a straw-yellow bile is flowing. One may say that the liver is responsible for this dark viscid bile. Two investigators cut out the gallbladder, and in this case from the beginning of the experiment they received thin bile which did not contain mucin. Therefore there is no doubt that the thick mucin-containing bile flowing through the fistula shortly after a meal is from the gallbladder. That is the first fact which is hard to accept from the point of view of Dr. Halpert's theory.

The second fact is about the bile passages. We must not look on the bile passages as in passive use. They are in active use. They may let the bile run into the intestine or into the gallbladder. There are two sphincters which may regulate the flow of the bile, one in the common bile duct and another probably in the wall of the cystic duct or in the neck of the gallbladder. This is not a supposition to account for our facts. The dog has a double permanent fistula, a Pavlov's fistula of the ductus choledochus and a fistula of the gallbladder. Before the experiment the bile flows from the fistula of the gallbladder. As soon as food is given, conditions change, but it makes a great difference what food is given. If milk or meat is used no bile flows from the gallbladder during the first three to four hours. All the bile is directed to the common bile duct fistula. Later on, in the fourth or fifth hour, it flows in both directions; toward the common bile duct fistula and toward the gallbladder. When bread is given, conditions are different. In the first hour only the hepatic bile is directed toward the common bile duct. Later on the bile is flowing in both directions.

The third fact is that the gallbladder has the property to expel its contents into the duodenum. I will not discuss the property of the gallbladder to contract, because it is a complicated problem, and has no direct relation to our discussion.

The evidences of the fact that the gallbladder delivers its contents into the duodenum are so numerous that we could spend a whole night talking about them. Many investigators have shown that. I myself have reported some experiments on cats showing that the gallbladder is empty and collapsed after a meal containing cream and egg yolk. Dr. Halpert said that the gallbladder is emptied occasionally in small quantities. In my cases one hour after a fat meal only one or two drops of bile were left in the cat's gallbladder. I have been so interested that I asked our x-ray man at McGill University, Dr. Brooks, how things were going there. He told me that after the injection of dye in the morning, the gallbladder shows a good shadow, and after a standard meal consisting of cream and egg yolk in two hours the gallbladder is emptied and the shadow disappears, and he added that one can sometimes see this in the colon the next day. It is difficult to explain these facts from the theory of reabsorption of bile. Then we must make a highly improbable supposition that certain stimuli increase the absorption so much that in this short period of one or two hours the bile from the gallbladder is reabsorbed. If one adds to this certain data concerning the influence of nerves and drugs on the gallbladder, it will be seen that it is difficult not to believe that the contents of the gallbladder may be expelled into the duodenum. I would say that anybody who would like to say that this is not so will have a difficult task to prove that it is wrong.

I considered my invitation to address the members of these societies seriously, and therefore thought I would spend the time between when it was received, which was only about a week and a half, and this evening in trying to repeat experimentally Dr. Halpert's work. One fact in Dr. Halpert's work especially impressed me. His experiment with methylene blue is remembered. The methylene blue disappeared from the hepatic duct practically after thirty hours, but he could find the methylene blue in the gallbladder in something like seventy-two hours. Now, through what way had methylene blue reabsorbed from the gallbladder left the body? Did it get into the hepatic bile or into the urine to disappear completely? Maybe this bile had a third way to pass, and the third way was into the intestine. I performed the following experiments, only a few of which I shall quote. They answer this question of the bile passing into the intestine with a positive yes. The

first experiment was on a cat. With the animal under anesthesia, 6 cc. of 1 per cent methylene blue was injected into the gallbladder. The cat was left for six hours. After six hours the cat received 100 Gm. of cream and one egg yolk; then after two hours and twenty minutes, the cat was opened. The gallbladder was collapsed and almost empty. Two-tenths cubic centimeter of bile could be obtained from the gallbladder. The content of the first part of the duodenum consisted of yellowish-white masses. Further on there were greenish masses; so it could be interpreted that these experiments showed that bile from the gallbladder had already passed along and that later on hepatic bile poor in methylene blue was discharged.

The second cat received an injection of methylene blue. After five hours and twenty-five minutes, it received the same amount of cream and one egg yolk as the first cat. This cat did not eat the meal properly; she left part of it. The cat was opened about an hour and fifteen minutes after the test meal. The duodenum was filled with greenish-white masses. The common bile duct was cannulated. It could be seen that the bile which was flowing was dark green. This bile could be from the gallbladder or from the liver. The cystic duct was tied. Then this dark green bile was replaced by light brown bile. A remarkable phenomenon was observed: as soon as the light brown bile was placed in a cylinder and shaken with air, it turned green, and when the concentration of dye in both biles was compared it was found that it was about 2.4 times greater in the first bile than in the second. In other words, the first bile came from the gallbladder and the second bile from the liver.

The third experiment was done on a dog. Under anesthesia 5 cc. of bile was removed aseptically from the gallbladder (the gallbladder contained about 6 or 7 cc. of bile) and 5 cc. of 1 per cent methylene blue was injected. The next morning the dog was given a test meal of 250 cc. of cream and two egg yolks. After two hours and fifteen minutes the dog was opened under anesthesia. The gallbladder contained only 2 cc. of bile. The contents of the intestine was milkish yellow. This experiment could be interpreted in the sense of Dr. Halpert that the green bile with methylene blue was absorbed in the gallbladder and yet the fresh bile from the liver was flowing in the intestine. Hydrogen peroxide was added to the intestinal contents and the content turned green, but it was not yet proved that it was methylene blue because the bile under the influence of peroxide turned green (bilirubin could be converted into biliverdin). Therefore according to the method of Halpert lead acetate was added to this greenish content of the intestine, and after a certain time a light blue appeared which indicated that the dye injected into the gallbladder appeared in the intestine. I want to say only a few words about the reduction of the methylene blue. Apparently we have made an interesting observation that the bile removed from the gallbladder and mixed with methylene blue retains its green color for many days. I have had one such bile for seven days. The hepatic bile has the property to reduce methylene blue to a leuko-form. In the freshly secreted bile from the hepatic duct it seems there are substances which are able to reduce the methylene blue, and in the gallbladder bile there are certain substances which resist this reduction.

The last word is about the experiments on rabbits. One rabbit was given intravenous injections of methylene blue and left for five hours without food and then killed. The gallbladder was found to be practically empty; it contained less than 0.1 cc. of bile. Another rabbit was given injections with methylene blue also, but received food afterward. It was killed six hours later. The gallbladder contained 0.3 cc. of green bile only. The intestinal contents were yellow, but at that time the idea of reduction had not occurred. I must say the rabbit is a peculiar animal because its stomach is like that of no other animal. Its stomach is always filled with food, and it is constantly secreting pancreatic juice. Special experiments must be done to clear up the problem of discharge of the bile from the gallbladder into the duodenum in rabbits. My experiments show only that in both rabbits the gallbladders were practically empty. It is doubtful, however, whether the rabbit's gallbladder would react differently from that of other animals.

BÉLA HALPERT: I spoke of experiments with methylene blue in the rabbit and mentioned also the monkey. I may add to this that the experiment was performed once in man also, with a result much like that in the rabbit. Methylene blue was given by mouth in an amount used in the rabbit experiments, i. e., 20 mg. per kilogram of body weight to a woman, aged 37, on whom an operation was to be performed. One half of the dose was given eighty-six and the other seventy-four hours before laparotomy. The patient was kept on the usual hospital diet. The urine became free from methylene blue thirty-six hours before the operation. The bile removed from the gallbladder at operation, seventy-four hours after the last dose of methylene blue, contained the dye in a concentration (1 : 4,800) higher than in any of the similar experiments in rabbits.

STUDIES ON "MALIGNANT SCLEROSIS" OF THE KIDNEYS (FAHR). PAUL KLEMPERER and S. OTANI.

The studies were based on eighteen cases observed at Mount Sinai Hospital, New York City, and ample control material. In the cases studied, ten patients were males and eight were females. Seventy-two per cent of the patients were less than 50 years of age, while 28 per cent were older; this was exactly the reverse of the age incidence in sixty-two cases of benign sclerosis. The frequency of malignant sclerosis was evidenced by the fact that 34 per cent of all fatal cases of renal disease observed during the last two years were of this kind.

The essential clinical feature was hypertension of long duration with suddenly developing renal insufficiency which quickly led to the death of the patient. In two cases high blood pressure was incidentally discovered at the examination for life insurance. In the other instances, more or less severe symptoms, mostly headaches, failing vision, nosebleed or cardiac manifestations had caused the patients to consult a physician who had detected hypertension. Occasionally, the long duration could be concluded only from the marked hypertrophy of the heart, found at necropsy. The sudden occurrence of such serious symptoms as persistent vomiting, coma or stupor was the usual cause of the hospitalization of the patients. The duration of the terminal phase was from five days to five months; the average duration of all cases was thirty-nine days. The course of the disease in the terminal phase was always progressive, never was there a remission, and the patients died invariably despite every treatment. The clinical symptoms in fourteen cases were those of uremia — persistent vomiting, muscular twitchings, severe pruritus, restlessness and finally coma. The retention of nitrogen was extreme, values over 100 mg. urea nitrogen per hundred cubic centimeters of blood being the rule. In two of the remaining four cases without clinical symptoms of uremia, the figures of the urea nitrogen of the blood were over 100 mg. per hundred cubic centimeters of blood, proving the severity of the renal insufficiency. In the two other cases retention of nitrogen was present but was only moderate. Albumin, white cells and casts were always found, red blood cells were present in only a few cases. The specific gravity of the urine was always low with the exception of one case. When a concentration test had been done, it showed a low fixed specific gravity. Both the systolic and the diastolic blood pressure was always high, averaging 212/132 mm. Neuroretinitis was found in all cases with the exception of one in which the patient was not examined.

Macroscopically the surface of the kidneys was characterized by grayish-yellow granulations over depressed red areas. Though the granulations were always present, there were variations in the degree of atrophy. Only a few of the cases showed marked diminution in size, the average weight of all being 112 Gm. In every case petechial hemorrhages were seen on the surface and also on section; in three instances they were so numerous that the surface appeared riddled with smaller and larger hemorrhagic spots. The cross-section showed variations in the width of the cortex corresponding to the degree of atrophy, but the cortical markings were nearly always somewhat indistinct. There were always hemorrhages in the pelvic mucosa. Arteriosclerosis of the renal artery was conspicuous in only eight cases; but the arciform arteries appeared to be arteriosclerotic in the majority.

Coarse arteriosclerotic scars on the convexity of the kidneys, causing irregularities, were superimposed on the diffuse fine granulations in the majority of cases.

The histologic examination with low magnification showed various degrees of glomerular fibrosis and connective tissue replacement of the renal parenchyma. But even in the cases with marked fibrosis it was surprising to find that the majority of the glomeruli did not present prominent morphologic changes. In order to obtain a numerical measure, the glomeruli in fields of equal size were counted and classified according to the degree of morphologic alteration. Thirty-eight per cent showed such definite changes as complete or partial fibrosis, necrosis of the capillary tufts, epithelial or endothelial proliferation. The remaining 62 per cent appeared unaltered apart from collapsed capillaries as an evidence of a disturbance of their blood supply. The fibrosed malpighian corpuscles differed in no way from those found in arteriosclerosis of the kidney. There could be observed the various stages and modes of development of fibrosis, as collapse and fusion of loops, hyalinization and capsular thickening with gradual choking of the glomerulus. In nearly half of the damaged glomeruli severe degenerative and seemingly inflammatory changes were observed. The former were hyaline droplet degeneration of the internal and external capsular epithelium and necrosis of the capillary loops. The latter consisted of endothelial and epithelial proliferation with even occasional formation of crescents as in the extracapillary forms of subacute glomerular nephritis, accumulation of polymorphonuclear leukocytes within the capillary lumen and Bowman space, here often mingled with desquamated epithelium and occasional red blood cells. The glomerular alterations were not missed in any of the cases though there were variations in their frequency in the individual observation. However, it appeared logical to conclude from the percentage of their occurrence that the actual glomerular damage could not be held responsible for the severity of the renal insufficiency.

Furthermore, it was questioned whether the nuclear increase and epithelial proliferation within the malpighian corpuscles should be considered as actually inflammatory as Fahr believes, or merely as a reaction to ischemia. The presence of similar changes in severe renal arteriosclerosis (the benign decompensated sclerosis of Fahr) seemed to favor the latter view. The observation of identical glomerular changes in the periphery of recent bland renal infarcts was considered as further support for the view that they represented a reaction to ischemia. The glomeruli in such locations showed also clearly hyaline droplet degeneration which Fahr maintains to be toxic in origin. There could not be any doubt of the ischemic etiology in such instances as renal infarcts. The occurrence of these questionable glomerular changes, therefore, could not be considered as proof of the inflammatory nature and toxic origin of the malignant sclerosis.

The most outstanding changes, however, were not those of the glomeruli but necrosis of the arterioles and cellular intimal proliferation of the distal portions of the interlobular arteries. These observations were in full accord with Fahr's description. The interpretation of these results, however, differed again from that of Fahr. He considers the arteriolar changes as inflammatory in nature, and toxic in origin and terms them necrotizing arteritis and arteriolitis. The reason for his conception is the occurrence of arteriolar-necrosis in subacute glomerular nephritis which changes he identifies with the arteriolar lesions in malignant sclerosis. However, our observation in several cases of subacute glomerular nephritis with severe arteriolar changes did not confirm Fahr's contention of their identity with the arteriolar-necrosis in malignant sclerosis. The arterioles in subacute glomerular nephritis showed not only necrosis but always intravascular and perivascular accumulation of polymorphonuclear leukocytes which were completely absent in the necrotic arterioles of our group. It was, therefore, correct to speak of necrotizing arteriolitis in subacute glomerular-nephritis but the term was not justified in the cases of malignant sclerosis observed by us.

Since glomerular changes as described by Fahr were found in simple ischemic conditions, it was logical to search here also for arteriolar-necrosis which was actually found in the vasa afferentia in the periphery of a recent bland infarct. This proved that arteriolar-necrosis can be an ischemic phenomenon.

The cellular intimal proliferation in small arteries has been considered by Fahr as productive endarteritis. If we followed the entire course of such interlobular arteries in serial section, we could observe that the proximal portions of the artery showed lamellations of the internal elastic membrane in the outer, and a cellular layer in the inner zone of the proliferated intima which was characteristic of arteriosclerosis. The distal portions, however, showed no elastica lamellations. It seemed, however, difficult to believe that the same vessel should be involved in two different pathologic processes, namely, arteriosclerosis in the proximal and endarteritis in the distal portions. It seemed rational to conclude that the cellular intimal proliferation was also arteriosclerotic in nature, the more so because no definite inflammatory reaction, such as intravascular or perivascular infiltration, could be observed in our cases. The proliferated cells suffered severe hyaline degeneration and fatty infiltration. The presence of foam cells next to the lumen caused marked narrowing, occasionally complete closure. The histologic picture suggested a rapid intimal proliferation with acute secondary degenerative changes. This acute narrowing could well have been responsible for ischemic changes in the arterioles and glomeruli and explained satisfactorily the ensuing circulatory disturbance of the remaining glomeruli. The arteriolar-necrosis and the glomerular changes are conspicuous features which permit the diagnosis of malignant sclerosis, but they are not of primary pathogenetic significance. They are not conclusive of an inflammatory origin of the renal disease. In fact, they are only secondary to a rapidly developing arteriosclerosis (Löhlein) of the interlobular arteries.

The term malignant sclerosis should be supplanted by such a clinical or anatomic descriptive name as "chronic hypertension with acute uremia or arteriolosclerosis —and necrosis of the kidneys."

DISCUSSION

ARTHUR M. FISHBERG: I cannot refrain from expressing to Dr. Klemperer and Dr. Otani the great pleasure I have had in listening to their splendid presentation. As far as terminology is concerned, I think the terms benign and malignant sclerosis are scarcely apt. These cases of so-called malignant sclerosis start as essential hypertension. In every one of the cases we have seen, the patient has shown evidence of having had hypertension of many years' duration. There was always marked cardiac hypertrophy. In other words, the process of arteriolar necrosis, which characterizes anatomically the so-called malignant sclerosis, is merely a complication of essential hypertension, and it is by no means the most frequent complication. The most common complication is cardiac failure. The second most frequent complication is cerebral hemorrhage, and the third is renal insufficiency which may or may not be due to arteriolar necrosis. For these reasons, I think a better term to use for the cases with arteriolar necrosis would be the malignant phase of essential hypertension. These patients have had essential hypertension for years, twenty in one of our cases, and the period characterized clinically by renal insufficiency and anatomically by arteriolar necrosis is merely one phase, the last.

Arteriolar necrosis is not the only cause of renal insufficiency in essential hypertension. There are at least three causes. One of these is the coalescence of the arteriosclerotic foci of atrophy in the kidney until so little intact parenchyma is left that the patient dies of uremia. Such patients are generally old. The second cause is cardiac failure, usually due to coronary disease, in patients whose concentrating power has already been moderately impaired. The third cause is the superimposition of arteriolar necrosis in the kidney.

It is perhaps worthy of emphasis, because of some recent statements in the literature, that the appearance of hypertensive retinitis in a patient with essential hypertension is not proof that there is arteriolar necrosis in the kidneys. I have seen cases of essential hypertension in which hypertensive retinitis developed, but at necropsy only "benign" changes were present in the renal arterioles.

Finally, I should like to add one more argument for the conception advanced by Dr. Klemperer and Dr. Otani that arteriolar necrosis is pathogenetically closely related to arteriolosclerosis, being presumably a more acute form of the latter.

It is known that arteriosclerosis has a characteristic distribution, being most marked in the kidneys; less so in the pancreas, spleen (here hyalinization of the arterioles is physiologic), liver and a few other organs; and totally absent in the voluntary muscles, though found extremely rarely in the myocardium. Arteriolar necrosis has this distribution, which would speak for a close relationship between the two processes.

HERMAN O. MOSENTHAL: We owe a debt of gratitude of more than the conventional sort to Dr. Klemperer for having worked up these cases which are among the first to demonstrate the presence of these lesions. I sincerely agree with Dr. Fishberg in regarding these pathologic changes as another example of the serious effects which hypertension has on the various organs. Dr. Klemperer has shown us that this necrotizing arteriosclerosis of the kidneys occurs in patients who had been the subject of hypertension for a long period, and what I believe is equally important and of great significance is that there was a rise in the diastolic as well as in the systolic pressure in these cases. This leads me to one other point, which is this: It seems to me that the term malignant in connection with hypertension is an extremely unfortunate one. In the first place, according to various students of this subject, it is applied to three distinct complications accompanying high blood pressure; thus its significance from either the pathologic or the clinical point of view is not clear. Furthermore, the terms malignant and benign are usually used in medicine in describing conditions entirely apart from a disease like essential hypertension. I believe it would be much more appropriate if the terms malignant and benign were dropped in this connection, and if we would simply classify these cases as mild or severe, and the criterion for such a classification would be the height of the diastolic pressure. Any patient with a diastolic pressure constantly at a level of about 130 mm. of mercury or above should be classed as a severe instance of essential hypertension, with the idea in mind that within a comparatively brief space of time there will develop in him lesions in the heart, brain or kidneys that will prove to be fatal. The diagnosis of the site of the pathologic change and its character, of course, cannot be made until the pathologic lesions actually develop. Dr. Klemperer has, I believe, furnished exact data as to another form of chronic interstitial nephritis in a complete and satisfactory way. The fact that we can trace these serious lesions in the kidneys to a definite cause, that is, a mechanical strain entailed by an increased blood pressure, is significant and adds a new feature to the etiology of acute diseases of the kidney.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, May 13, 1929

ESMOND R. LONG, *President, in the Chair*

THE VALUE OF CULTURE IN THE DIAGNOSIS OF TUBERCULOSIS. H. C. SWEANY and MAX EVANOFF.

After several years of experimentation with culture mediums, we are able to recommend a method or combination of methods by which practically all viable tubercle bacilli can be grown. The percentage of positive results is slightly higher than that obtained by animal inoculation. Obviously, such procedures have greater value in diagnosis and save time and expense.

The growth becomes visible within two or three weeks, but acid-fast bacilli may be demonstrated within a week in stained preparations. The cost of a culture diagnosis does not exceed 20 cents, while a fair charge for diagnosis by animal inoculation is $4.

There are a few rare lesions with cultural results not comparable to those with animal inoculation. In old fibrous lesions with attenuated bacilli and in some primary lesions of children, we have encountered difficulty in culturing tubercle

bacilli. Sometimes, we have failed to obtain growth when the material is overgrown with spore-forming bacilli. Success in such circumstances depends largely on the technic of treating the material with caustics.

Summarizing the results in the cultivation of human tubercle bacilli from lesions in man, we obtained the best growth with our "cream" medium and nearly as good with the "milk" medium. Both were better than Petroff's egg and Corper's potato mediums. With twenty-two lesions of various types and stages of healing, in which a diagnosis could not be made directly, growths were obtained by culture in 55 per cent and by animal inoculation in 35 per cent. There is little doubt that many of the lesions were entirely closed so that the true percentage for viable tubercle bacilli probably is much higher.

The germicides of choice are 3 per cent hydrochloric acid and 3 per cent sodium hydroxide, respectively, applied for from twenty to thirty minutes. While it is true that all acid-fast bacilli may not be tubercle bacilli, all of the numerous acid-fast micro-organisms that we have grown from material from man have the pathogenicity of tubercle bacilli. It is safe, therefore, to make a tentative diagnosis of tuberculosis by finding slow-growing, cribriform, waxy colonies of acid-fast bacilli.

From bovine tuberculous lesions we have commonly found acid-fast and semi-acid-fast micro-organisms that do not have the usual pathogenicity of this variety of tubercle bacilli. In fact, by our method of direct culture from the lesions it seems that there is a wide variation in strains of different lesions which diminish in virulence to saprophytes. Bacilli of high virulence seem to be obtained consistently only after passage through animals in which the associated weak forms appear to be overgrown by the virulent forms. For this reason, perhaps, our virulence tests do not correspond to those of Park. Some of these atypical strains appear to regenerate into the usual forms, while others are saprophytes. The early colonies of bovine tubercle bacilli on our cream medium sometimes appear soft and spreading, but assume the more crumblike form as they become older. Another striking feature concerning the bovine type is that no growth was obtained directly from seventeen lesions on medium containing fresh glycerin, but organisms in these grew on our cream medium without glycerin. This feature has been observed by Park and others with recently isolated bacilli, but not from true primary cultures. The bovine tubercle bacilli gradually gain avidity for glycerin when they are passed through guinea-pigs and are cultured.

The tubercle bacilli obtained from three lesions from hogs simulated, but were not identical with, those obtained from lesions from fowls. There seems to be a greater variation in the gross appearance of the avian forms than of the other types. The one diagnostic characteristic seems to be their ability to grow readily on practically all standard mediums for culturing tubercle bacilli. Confirmation by the usual pathogenicity tests is necessary.

LIPOSARCOMA OF THE MAMMARY GLAND. RICHARD A. LIFVENDAHL.

The rare occurrence of a liposarcoma of both mammary glands is here reported.

An Italian woman, aged 41, four months after the delivery of her fifth child, noted small soft masses in both breasts, which increased slightly in size for four months before her admission to the Cook County Hospital. The infant was nursing when the patient was admitted, and no general symptoms were present. Both mammae were removed without the pectoral muscles or the axillary lymph nodes.

Both glands were covered by coarsely wrinkled skin that had from ten to fifteen various sized nodular elevations of smooth contour. The nipples were not retracted and were without abnormal discharge. In the tissues were from ten to fifteen round and ovoid masses which involved three fourths of the right and one fourth of the left breast. They were located at various depths, none was adherent to the overlying skin and all were well circumscribed from the remaining yellow and grayish-white mammary tissue. They were composed of grayish-white and pale yellowish-white, moderately firm tissue, containing a glairy, colorless, mucoid liquid. There were small hemorrhages in one of the nodes of the left breast. The

cytoplasm of the cells in the nodes contained lipoid droplets. The cells varied markedly in size and shape; many were round or oval, and still others were spindle-shaped. The nuclei of those containing much lipoid were at the periphery and were eliptical. Some of the cells contained two nuclei and some were in mitosis. The stroma consisted chiefly of a loose myxomatous tissue with widely separated various sized spindle cells containing various quantities of lipoid.

The relatively normal tissue surrounding the tumor masses consisted of grayish-white streaks and bands with interspersed yellow material. These regions contained alveoli, some with large quantities of secretion. The ducts near the tumors were slightly flattened, and the intervening stroma was scanty.

The patient left the hospital; she died within three months after the mammectomy from what seemed clinically to be metastases of the lungs.

THE EARLY AND THE HISTOLOGICALLY HEALED END-STAGES OF PERIARTERITIS NODOSA. AARON ARKIN.

Periarteritis nodosa is a specific infectious disease probably caused by a filtrable virus, with an elective affinity for the arteries of the body. The organs most commonly involved are the kidneys, heart, liver, muscles, peripheral nerves and gastro-intestinal tract. Any organ or all may be affected.

The chief symptoms are a septic temperature, polyneuritis and polymyositis, hematuria or nephritis, abdominal cramplike pains and progressive emaciation. The great variability of the symptoms, pointing to involvement of various organs, and the tendency toward acute exacerbations are suggestive of periarteritis nodosa.

The pathologic changes hitherto described may be divided into three stages: (1) alterative-degenerative, (2) acute inflammatory and (3) granulation tissue. In practically all published accounts various stages of these changes are recorded in different organs. I have studied five cases of the disease.

In one acute case, the earliest change was a periarteriolar hemorrhage, probably due to an increased permeability of the endothelium. In other small arterioles, there were edema and fibrinous exudation without leukocytic infiltrations. The subintimal fibrinous or hyaline-like exudation often narrows or obliterates the lumen of the vessel. The fibrin may extend through the intima into the lumen of the vessel. In the larger arteries the changes often begin around the elastica externa. Later, leukocytes appear.

My report concerns the histologically healed end-stage, or scar tissue stages, of periarteritis. A patient, aged 26, suffered from a single severe illness with icterus, high fever, acute nephritis and hematuria. He died four years later of renal and cardiac insufficiency. The postmortem examination revealed a histologically healed periarteritis nodosa affecting all the organs of the body except the central nervous system. The contracted kidneys, hepar lobatum, myocardial scars, pancreatic and suprarenal gland atrophy and coronary stenosis were due to this disease.

Cardiac insufficiency which fails to react to digitalis, renal insufficiency with low specific gravity and reduced chlorides of the urine, progressive emaciation, abdominal pain and hepar lobatum have not been ascribed to this disease. Although the right and left coronary arteries were reduced to one-fourth their normal caliber, there were no symptoms of angina pectoris.

The characteristic histologic changes found were: (1) proliferation of the intima with the new formation of elastic fibrils, leading to stenosis or even complete occlusion of the arteries; (2) extensive destruction of the media, including the elastica interna or the entire wall of the vessel, with aneurysmal dilatation and thrombosis, and subsequent complete organization; (3) a periarterial healed granulation tissue mantle, consisting of dense fibrous connective tissue with capillaries and deposits of hemosiderin; (4) extensive destruction and even aneurysms in arteries with marked proliferation of the intima; (5) healed infarct scars of most organs, and (6) marked stenosis of both coronary arteries with destruction of their walls.

The hepar lobatum and extensive scars in different organs (due to infarction from arterial occlusion) demand a careful study of the arterial changes. Certain

livers, scarred like those in syphilis, may be so changed because of periarteritis nodosa. Elastic tissue stains should always be made.

AN ANALYSIS OF THE NECROPSY STATISTICS OF A SECTARIAN HOSPITAL. O. T. SCHULTZ.

For the purpose of this presentation, sectarian hospitals are defined as those supported in whole or in large part by religious denominations. Christian has criticized hospitals supported by Jewish charity because of their supposed low percentage of necropsies, and similar criticism is directed also against those supported by Catholic organizations. The inference is that religious prejudice against necropsies is an important factor in the percentage figures for necropsies of such institutions.

At the Michael Reese Hospital, the percentage of permission for necropsy, which had been from 10 to 13 per cent up to 1921, increased suddenly in 1922 to 35 per cent and rose progressively to 56 per cent in 1927. The present hospital administration deserves a large share of credit for the sudden and continuous increase. The figures for 1926 and 1927 have been subjected to analysis in an attempt to determine, if possible, what factors, including the element of religion, may interfere with the gaining of permission for postmortem examinations. For such an analysis the necropsy service of the Michael Reese Hospital lends itself

TABLE 1.—*Percentages of Necropsies by Services*

	Ward			Private			Total		
	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage
Pediatrics	272	200	74 (79)	105	47	45 (53)	377	247	66 (78)
Medicine	96	39	41 (42)	135	37	27 (30)	231	76	33 (36)
Surgery	94	48	51 (55)	108	45	42 (51)	202	93	46 (53)
Gynecology and obstetric...	24	8	33 (31)	24	9	38 (50)	48	17	35 (38)
Total	486	295	61 (64)	372	138	37 (44)	858	433	50 (56)

well because: it is a general hospital of 557 beds; it is supported by the Associated Jewish Charities of Chicago; it combines both charity and private services (approximately 60 per cent of its work being charity); it is open to reputable physicians not members of its staff, and staff membership is not limited exclusively to physicians of Jewish faith. The religious belief of the patient is not a factor in his admission to the hospital. During 1926 and 1927, about 57 per cent of the patients were Jewish, the proportion being approximately the same for both charity and private patients. It is possible, therefore, to compare the necropsy percentages within the same hospital of both private and charity, and Jewish and non-Jewish patients.

The data which have been studied relate to 189 necropsies done in 1926, for which year the permission percentage was 45, and to 244 necropsies done in 1927, when the percentage was 56, a total of 433 necropsies in two years, which constituted 50 per cent of the deaths.

In table 1, the data are arranged according to services, the figures for 1927 alone being given in parentheses. The striking difference between the ward and the private services is apparent at once. Fifty-seven per cent of all deaths occurred in ward patients, but this number yielded 61 per cent of necropsies, whereas 43 per cent of deaths of private patients yielded only 37 per cent of necropsies. Also striking in this table is the high percentage for pediatrics, and the appreciably larger proportion of necropsies in surgical as compared with medical patients.

To determine if sex is a factor, the figures for adults, arranged according to sex, are given in table 2. Adult deaths made up 52 per cent of the total deaths in the hospital, and 54 per cent of the total adult deaths occurred in females.

There is no significant difference in the percentage of necropsies in deaths of adult male and female patients.

A comparison of the necropsy percentages in private patients of members of the hospital staff with those in private patients of physicians who are not members of the staff is given in table 3. At first glance the difference is not great enough to be significant in the mathematical sense, but it is actually greater than the mere percentage figures indicate, because 77 per cent of deaths of patients of staff members yielded only 36 per cent of necropsies, whereas 23 per cent of deaths of patients of nonstaff members yielded 39 per cent in necropsies.

The relation of religious faith to necropsy percentages, as given in table 4, is of greatest interest. A significant and striking difference is apparent in the necropsy percentages of both ward and private Jewish patients as compared with those of

TABLE 2.—*Sex (Adults)*

	Ward			Private			Total		
	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage
Female	104	43	41	137	49	36	241	92	38
Male	85	37	44	120	36	30	205	73	36
Total	189	80	42	257	85	33	446	165	36

TABLE 3.—*Private Patients of Staff and Nonstaff Members*

	Deaths	Necropsies	Percentage
Staff	288	105	36
Nonstaff	84	33	39
Total	372	138	37

TABLE 4.—*Religion*

	Ward			Private			Total		
	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage	Deaths	Necropsies	Percentage
Jewish	257	116	45	234	65	28	491	181	37
Non-Jewish	229	179	78	138	73	53	367	252	69
Total	486	295	61	372	138	37	858	433	50

non-Jewish patients. The difference is even greater than the table indicates, because the deaths of Jewish ward patients made up 53 per cent of all deaths of ward patients but furnished only 45 per cent of necropsies in this group. Sixty-three per cent of deaths of private patients occurred in those of Jewish faith, but permission for necropsy was obtained in only 28 per cent of such deaths. Necropsy was done in 181, or 37 per cent, of a total of 491 deaths of Jewish patients and in 252, or 69 per cent, of a total of 367 deaths of non-Jewish patients.

ENDOCARDITIS AS A SEQUENCE OF OSTEOMYELITIS. RUTH SISSON.

Metastatic infection of the valves of the heart from the diseased bone is occasionally referred to in accounts of osteomyelitis or of endocarditis as a possibility (Phemister, D. B.: Nelson's Loose-Leaf Living Surgery, 1928, vol. 3, p. 715. Aschoff, L.: Pathologische Anatomie, Jena, 1928, vol. 2, p. 29. Dyas, F. G.: Surg. Gynec. Obst. **7**:555, 1908. Romberg, E.: Lehrbuch der Krankheiten des

Herzens und der Blutgefässe, 1925, p. 574. Osler, William; and McCrae, Thomas: Modern Medicine, vol. 4, p. 466). Some such references apparently are due more to an effort to have nothing left out of lists of what may occur than to any definite information about this rare sequence. Many standard works on surgery do not mention the infection (Lexer-Bevan: General Surgery, 1908. Lewis, D.: Practice of Surgery, 1927. Garré, G., and Borchard, A.: Lehrbuch der Chirurgie, 1923. DaCosta, J. C.: Modern Surgery, ed. 9, 1925. Duplay, S., and Reclus, P.: Traité de chirurgie, 1890-1892). I have been able to find only a few reports, and these are all of endocarditis following acute, rather than chronic, osteomyelitis. In one case reported by E. Fraenkel and A. Sänger (Untersuchungen über die Ätiologie der Endocarditis, Virchows Arch. f. path. Anat. **108**:286, 1887), the disease of the right tibia of a boy, aged 13 years, was attributed to *Staphylococcus aureus,* and only the front mitral leaflet became infected. The observations reported by T. Kocher and E. Tavel (Chirurgische Infectionskrankheiten, Basel and Leipzig, 1895, p. 124) occurred in boys, aged 15 and 17 years. In the younger, the osteomyelitis affected the right tibia and all leaflets of the tricuspid valve were involved; in the older boy, the left internal malleolus was affected, as well as all the tricuspid and mitral leaflets. In both patients the organism was staphylococcus. Much more recently, W. S. Thayer (Studies on Bacterial [Infective] Endocarditis, Johns Hopkins Hosp. Rep. **22**:35, 1926), in a bacterial study of endocarditis, referred to staphylococcal valve lesions due to osteomyelitis or epiphysitis in four patients. The valves impaired are not specified.

On account of the long duration of the illness, the many remissions and for other reasons to which allusion will be made presently, it seems likely that the aortic endocarditis in the following case was metastatic from an osteomyelitis.

Clinical History.—A man, aged 46, fell 25 feet, breaking both bones of both legs. The fractures of the right leg healed uneventfully, but seventeen days after the accident it was found necessary to fix the fragments of the left tibia with ivory pegs. (For these clinical details I am indebted to Dr. C. R. G. Forrester and Dr. Leroy Kuhn of Chicago.) There was some fever after the operation, the temperature being 101 F. on the third day, with a gradual drop to normal on the tenth day. A Wassermann test of the blood for syphilis gave negative results. The patient left the hospital in good condition, but one month later there was a small wound of the front of the left leg which still drained.

Six months after the first operation, considerable infected bone was found with the roentgen rays where the fragments of the left tibia had been pegged together, and after a second six months, there were three open draining fistulous passages. A sequestrum was removed at this time, and the infected tissues were curetted. There was a slight fever for five days. The patient left the hospital at the end of three weeks.

Four months later the wound was still draining and small fragments of bone were removed. Two months after this another sequestrum and one of the bone pegs were removed, and the curetted cavity was filled with adipose tissue from one buttock. His stay in the hospital this time was six weeks. Two months later the wound was still draining, and there was considerable inflammation of the leg. For this condition he was once more admitted to the hospital for six weeks, where hot boric acid fomentations and other local treatment were applied which again resulted in an apparent cure. During this period, he had a fever which lasted about a week, the highest rise in temperature being 102.6 F.

Another serious operation was found necessary three months later, at which time the front of the tibia was chiseled away, and part of a bone peg was removed with considerable bone that was honey-combed with fistulous passages. After this procedure the patient remained in the hospital for three months. Intermittent discharge from the wounds continued for the next eighteen months, and four years after the first operation he became acutely ill with what was regarded as pneumonia and died. From the record of the postmortem examination and subsequent studies, the following points are important:

Necropsy (Dr. E. R. LeCount).—The anatomic diagnosis was: ulcer of the left leg; chronic osteomyelitis of the left tibia; large defect of the tibia; healed fracture of the left tibia and fibula (malunions); bony union between the shafts of the left tibia and fibula; hyperplasia of the left inguinal lymph glands; thrombo-ulcerative aortic endocarditis; multiple infarcts of the kidneys and spleen; embolic hemorrhages in the brain; acute hemorrhagic nephritis; hypertrophy of the left ventricle of the heart; hypostatic hyperemia of both lungs, and chronic catarrhal bronchitis.

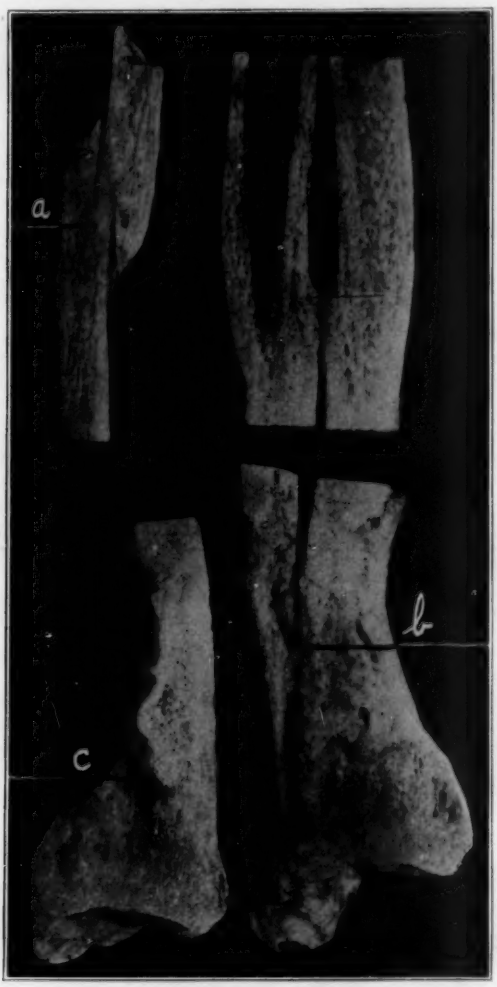

Fig. 1.—The lower end of the tibia and fibula, grown together, were sawed in a plane diagonally from in front back and out. The segment of the malunited fibula in the upper left hand corner has not been cut lengthwise. *a*, fibular malunion; *b*, bony union of the tibula and fibula; *c*, osteomyelitic cavity.

As a mass, the lymph glands of the left groin were twice the size of those of the right. No gross evidence of suppuration was found in them. There was an ulcer of the inside and ventral surfaces of the distal third of the left leg, which was 6.5 cm. long and from 10 to 15 mm. wide. Its distal end was 5 cm. above the

level of the malleoli, and its bottom was deep in a defect of the tibia. Sixteen centimeters above the distal end of the fibula, the lower end of the upper fragment made when the bone was broken lay on the outer surface of the upper end of the lower fragment. This overlapping was 3.5 cm. long, and the two fragments were firmly joined by compact bone. As a result the upper portion of the shaft of the fibula was completely out of vertical alinement with the distal part (fig. 1, *a*). Beginning 5.5 cm. above the distal end, the fibula was firmly united to the tibia for 4 cm. by compact new bone slightly more abundant externally and ventrally than behind (fig. 1, *b*).

The fracture in the tibia began about 1 or 2 cm. distal to that in the fibula and was healed without much deformation of the shaft. The defect in the tibia began 2 cm. from the articular surface for the talus, was 9.5 cm. long, shallow and indefinite at its proximal end and was deep distally (fig. 1, *c*). The bone lining this cavity was irregular, with shallow and deeper small pits, a fine mosslike network of superficial furrows and sharp brittle delicate spicules a few millimeters long in its deepest portion. The adjacent surfaces of two of the aortic leaflets

Fig. 2.—A microscopic preparation of the two most involved aortic valves, enlarged about 4 diameters. *a*, cocci along the ventricular edge; *b*, the common junction of the leaflets nearest the aorta.

were firmly grown together so that they had a common free edge for 7 mm. out from their joined commissure. Pink fibrin covered about one half of the ventricular surfaces of each of these cusps, and on the corresponding surface of the third cusp, that from the sinus where the front coronary has its mouth, there was a rough red place from 6 to 7 mm. in diameter. Infarcts, some with gray centers, occupied about two thirds of the surfaces made when the spleen was cut in different places. The spleen was 12 by 9.5 by 5.3 cm. One infarct in the right kidney was 20 by 11 mm. in two of its dimensions. One in the left was almost as large, and in this kidney there was also a smaller infarct; in both kidneys there were small hemorrhages.

Histology.—There were large masses of gram-positive cocci without any chain formation on the ventricular edge of the aortic leaflets (fig. 2, *a*) and smaller masses in other focal lesions of the brain, kidney and heart muscle. Those in the kidney were small, few and wide apart in the central parts of the infarcts and more abundant in the periphery, especially the edge toward the pelvis. There

were also minute foci (0.3 mm. in diameter) deep in the medullary pyramids where infarcts were absent. The focal lesions in the heart were widely scattered and very small; some occupied no more than the space taken by seven muscle fibers cut squarely across; other lesions of the heart consisted solely of scattered leukocytes in lesions less sharply demarcated. In the sections of the lymph glands of the groin on the affected side there was simply hyperplasia. In the suprarenal glands, liver, pancreas and other organs no noteworthy change was found.

There is no certainty that the infection of the heart owed its origin to the osteomyelitis. However, the frequent attacks of fever, the number of operations, the persistence of the infection of the leg, the absence of a history of any other illness from which the endocarditis might have had its origin, the failure to find any other disease in the body to which it might have been secondary and finally the staphylococcus nature of all of the lesions are strongly in favor of the mode of death suggested by the title and the anatomic diagnosis.

Book Reviews

PRINCIPLES OF PATHOLOGY FOR PRACTITIONERS AND STUDENTS. By D'ARCY POWER, M.D., F.R.P.S., Professor of Pathology, College of Physicians and Surgeons, San Francisco; and WILLIAM W. HALA, M.D., Assistant Professor of Pathology, Long Island College Hospital, Brooklyn. Price, $10. Pp. 787, with 298 illustrations, many in color. New York: D. Appleton & Company, 1929.

For the most part the book is built on the conventional plan of textbooks of pathology. It is divided into two main parts: general pathology and systemic pathology. Contrary to the usual custom, general disturbances of the circulation are considered under the vascular system in the special part, which includes all the organs except the eye and the ear. There is an appendix with notes on microscopic technic, photography, theory of cell heredity, the Ehrlich nomenclature, protein nomenclature, the biochemical reactions of the body and sedimentation of the erythrocytes. The index seems to be complete and accurate.

A peculiarity of the book is the division of the text into consecutively numbered sections, 1,077 in all, a system which was adopted to facilitate cross references. This is a good principle because much space may be saved by reducing more than customary the repeating of descriptions of the same processes in the section devoted to general pathology and in the various subdivisions of systemic pathology. The main characteristics of tuberculosis, for instance, are the same no matter what its location, and there is no real need for repeated descriptions of these characteristics.

It is easy to find more or less minor faults with this book, but the essential teachings may be regarded as acceptable. The main fault with the book is that it does not reflect sufficiently the best kind of scholarship in modern pathology. It does not represent any advance over existing books in its field in either the style of writing, the matter of illustration, or the choice and treatment of subjects. Many of the illustrations are crude, some are indistinct, and taken as a whole they fall short of reasonable modern requirements. The book does not appear to meet any need that is not fully met by other books.

DIE MORPHOLOGIE DER MISSBILDUNGEN DES MENSCHEN UND DER TIERE. Ein Hand- und Lehrbuch für Morphologen, Physiologen, Praktische Aerzte und Studierende, Herausgegeben von DR. G. B. GRUBER, o.ö. Professor der pathologischen Anatomie an der Universität Innsbruck. Unter Mitwirkung zahlreicher Fachgenossen, begründet von WEIL and PROF. DR. ERNST SCHWALBE. III. Teil: Die Einzelmissbildungen. XIII. Lieferung. 3. Abteilung. 4. Kapitel: Die Missbildungen des Darmkanals und der Verdauungsdrusen, Einschliesslich der Kloakenmissbildungen. Von PRIVATDOZENT DR. H. E. ANDERS. Paper. Price, 7.50 marks. Pp. 107, with 60 illustrations. Jena: Gustav Fischer, 1928.

Previous sections of Schwalbe's monumental work on "The Morphology of Monstrosities and Abnormalities of Man and Animals" have been reviewed in the ARCHIVES OF PATHOLOGY (**4**:504 [Sept.] 1927).

The present sections deal with abnormalities of the digestive tract, including the liver and pancreas. There is an introductory chapter on normal development, followed by a detailed consideration of the abnormalities of position, persistence of portions of the embryonal intestinal tract, defects of development, reduplications and gigantism, stenosis and atresias and finally congenital dilatation and diverticulation of the various parts of the gastro-intestinal tract. The final two chapters deal with the developmental disturbances of the pancreas and liver. There is a list of 372 references, most of which are to the German literature.

Many of the illustrations are schematic. The treatment of the various subjects is exhaustive and yet concise. Schwalbe-Grüber's work will for many years be the best reference book on the complicated but important subject of developmental faults.

DISEASES OF THE THYROID GLAND. By ARTHUR E. HERTZLER, M.D., Surgeon to the Halstead Hospital, with a chapter on Hospital Management of Goiter Patients by VICTOR E. CHESKY, M.D., Associate Surgeon to the Halstead Hospital. Ed. 2. Entirely rewritten. Price, $7.50. Pp. 286. St. Louis: C. V. Mosby Company, 1929.

The title is a little too comprehensive, as the book deals mainly with goiter and surgical treatment for this condition. There are ten chapters: etiology of goiter; normal anatomy of the thyroid gland; pathologic anatomy of the thyroid gland, dealing mostly with goiter; symptoms of goiter; diagnosis; prognosis and treatment; goiters in unusual places; hospital management of patients with goiter (by Victor E. Chesky); topographic anatomy of the thyroid gland, and operative technic. Chapter three, on pathologic anatomy, occupies seventy-seven pages and includes a summarizing description of carcinoma and sarcoma of the thyroid gland.

Goiters are classified as colloid, as adenomas or nodular goiter without toxic symptoms, as adenomas with toxic symptoms, and as exophthalmic goiter, all of which are interpreted as stages of one progressive disease. The gross and microscopic descriptions are brief and clear with a tendency to oversimplification. Graves' disease is defined as toxic goiter due to the abnormal activity of newly formed acini developing from interstitial cells, while the term Basedow's disease is limited to those cases of toxic goiter in which disease of the eye is present. Fetal adenoma is treated as a true tumor; it is given great importance as the main source of carcinoma of the thyroid gland, and for that reason its removal is recommended on the same general principle as the removal of moles may be recommended, as a precautionary measure. The author, who is a surgeon, is fascinated with his study in which he is concerned mainly in establishing the true relationship of the clinical manifestations of goiter to the structural changes in the thyroid gland, but he does not discuss the fundamental problems of the physiology, normal and abnormal, of the thyroid gland. The presentation throughout the book is of a general and summarizing character, and there are no records given of the results of the systematic and thorough study of individual cases.

The consideration of the interstitial changes in goiter is limited mainly to the following statement: "There is yet to be considered a peculiar type of gland that must be considered apart from the general subject of the pathology of goiter. The only excuse for considering them here is that they too often lure the surgeon into performing a useless operation. These represent the type which some internists correctly associated with a peculiar type of person; slender of build, delicate skeleton, vivacious rather than intelligent, often bright eyed, in short, the type of girl depicted in automobile advertisements. Their goiters are never large, are elastic rather than firm, generally located high up on their long slender necks. The goiter cuts like rubber and is finely granular in appearance. Microscopically, the striking feature is the abundant lymphocytic infiltration and large number of lymph follicles. In a previous publication I expressed the opinion that they never contained germinal areas, but I have since seen specimens in which they were present. In addition, lymph glands the size of a bean are commonly found in the carotid group of lymphatics. This type may be called interstitial, for what little cellular changes they show is in the interstitial cells. The striking part of the picture is the flatness of the acinal epithelium. The increase of the colloid is never great, corresponding to the fact that in the clinic the thyroid gland is seldom larger than what one may describe as easily palpable, the impressive change being in the greater firmness of the gland. With such a picture one need not be surprised that little or no improvement is gained from operative removal of a part of the thyroid. Since this type is so generally associated with menstrual

disturbances, it seems that it should not be regarded as a thyroid disease at all, but merely a part of a general endocrine disturbance. In the severer cases there is an associated aplasia of the ovaries, and probably also a pituitary deficiency as well."

The author states his belief that the relationship set forth will gain recognition with time. The question of the influence of iodine on the structure of toxic goiter is not discussed, but in the preface reference is made to the work of Alexander Hellwig on this problem (*Surgery, Gynecology and Obstetrics with International Abstract of Surgery* **47**:173, 1928), using material from the author's clinic. The illustrations in the book are creditable.

ETIOLOGIE ET PROPHYLAXIE DE LA GRIPPE. By R. DUJARRIC DE LA RIVIÈRE. Monographs of the Pasteur Institute. Price, 32 francs. Pp. 105, with 15 illustrations. Paris: Masson & Cie, 1929.

The author has presented this short readable monograph on the subject of influenza, apparently with an idea of bringing together current opinions and ideas on technic, more or less as a basis for future work. The book is divided into a short introduction covering the epidemiology, a major chapter on Pfeiffer's bacillus, a general chapter on the concept of the filtrable virus, and a discussion of the prophylaxis. A bibliography of 221 references is included, apparently fairly complete but poorly arranged. The fifteen excellent double photographic plates show the morphologic, microscopic and macroscopic aspects of Pfeiffer's bacillus and also several other hemoglobinophilic species.

The discussion of the epidemiologic phases is evidently intentionally cursory. In his discussion of Pfeiffer's bacillus, some emphasis is laid on the technic of isolation with which the author is familiar. The necessity for blood, the considerations of growth accessory factors, and the general cultural details are carefully described. Discussion of the pathogenicity of this organism covers most of the common laboratory animals and also experimental work on monkeys and on man. Serologic characteristics are briefly discussed, together with the means of identifying Pfeiffer's bacillus among the group of hemoglobinophilic bacteria with which it might be confused. In discussing the possible filtrable virus of influenza, the author apparently attempts to list impartially arguments for and against this etiologic agent. The chapter is carefully completed by discussing in some detail the *Bacillus pneumosintes* of Olitsky and Gates, and also by discussing the possibility of the filtrable forms of Pfeiffer's bacillus. He mentions that the proof of true filtrability is often lacking. His discussion of prophylaxis contains virtually nothing new.

If the reader of this monograph has not been converted to any one of the theories of influenza, he is left with the impression that Pfeiffer's bacillus perhaps merits more respect than it has been given in many quarters and that the author of this monograph perhaps has not given theories, other than that the etiologic agent of influenza is the Pfeiffer's bacillus, all the opportunities that they should have.

Books Received

METHODS AND PROBLEMS OF MEDICAL EDUCATION (Twelfth Series). Departments and Institutes of Roentgenology and Radiumtherapy. New York: The Rockefeller Foundation, 1929.

These bulletins are intended for distribution to teachers and administrators in medical schools and hospitals. Separate reprints and a limited number of volumes are distributed gratis to other interested persons on application to the Rockefeller Foundation, 61 Broadway, New York.

ABSTRACTS OF THESES, UNIVERSITY OF CHICAGO SCIENCE SERIES. Volume 6. Pp. 376. Chicago: University of Chicago Press, 1927-1928.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. Volume 12. Pathology of the Acute Respiratory Diseases and of Gas Gangrene Following War Wounds. Prepared under the direction of Major Gen. M. W. Ireland, Surgeon General. By Major George R. Callender, M.C., and Major James F. Coupal, M.C. Price, $3.60. Pp. 583. Washington, D. C.: U. S. Government Printing Office, 1929.

SEVENTEENTH ANNUAL REPORT, MEDICAL DEPARTMENT, UNITED FRUIT COMPANY. Pp. 381. Boston: 1928.

A HISTORY OF THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. By P. M. Ashburn, Colonel, Medical Corps, U. S. Army, author of "The Elements of Military Hygiene." With an introduction by Surg. Gen. Merritte W. Ireland. Price, $5.00. Pp. 448. Boston: Houghton Miffin Company.

PRINCIPLES AND PRACTICE OF ELECTROCARDIOGRAPHY. By Carl J. Wiggers, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland. Price, $7.50. With 61 illustrations. St. Louis: C. V. Mosby Company, 1929.

CLINICAL LABORATORY METHODS. By Russell Landram Haden, M.A., M.D., Professor of Experimental Medicine, University of Kansas, School of Medicine, Kansas City, Kan. Third edition. Price, $5.00. Pp. 317, with 69 illustrations and 4 color plates. St. Louis: C. V. Mosby Company, 1929.

A MANUAL OF EXTERNAL PARASITES. By Henry Ellsworth Ewing, United States Bureau of Entomology. Price, $4.50; by mail, $4.66. With 96 illustrations. Springfield, Ill.: Charles C. Thomas.

COLLECTED STUDIES FROM THE BUREAU OF LABORATORIES, Department of Health, City of New York. Dr. William H. Park, director. Volume 10, 1920-1926. New York: Department of Health.

THE CLINICAL ASPECTS OF VENOUS PRESSURE. By J. A. R. Eyster, B.S., M.D., professor of physiology, University of Wisconsin, associate physician, Wisconsin General Hospital, Madison, Wis. Price, $2.50. Pp. 135. New York: The Macmillan Company, 1929.

HUMAN HELMINTHOLOGY. By Ernest Carroll Faust, Ph.D., professor of parasitology in the College of Medicine of Tulane University, New Orleans. Cloth. Price, $8.00, net. Pp. 616, with 297 illustrations. Philadelphia: Lea & Febiger.

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT. Im Auftrage des Vorstandes herausgegeben von dem derzeitigen Schriftführer, G. Schmorl, in Dresden. Vierundzwanzigste Tagung gehalten in Wien, 4-6, April, 1929. Pp. 388, with 149 illustrations. Jena, Austria: Gustav Fischer, 1929.

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Manuscripts for publication, books for review, and correspondence relating to contributions should be sent to Dr. Ludvig Hektoen, 637 South Wood Street, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF PATHOLOGY, American Medical Association, 535 North Dearborn Street, Chicago.

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Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

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